CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-453

Generic Name: Lidocaine and Prilocaine Cream, 2.5%/2.5%

Sponsor: Altana Inc.

Approval Date: August 18, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-453

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter(s)	
Final Printed Labeling(s)	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

ANDA 76-453

AUG 18 2003

Altana Inc.
Attention: Audrey Zaweski
60 Baylis Road
Melville, NY 11747

Dear Madam:

This is in reference to your abbreviated new drug application dated July 1, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to your amendments dated February 4, March 18, April 28, June 18, July 8, July 14, July 24, July 29, July 30, July 31, August 7, and August 11, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Lidocaine and Prilocaine Cream, 2.5%/2.5%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (EMLA® Cream, 2.5%/2.5%, of Astrazeneca LP).

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

Post-marketing reporting requirements for this abbreviated application 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Validation of the regulatory methods provided in this application has not been completed by agency field personnel. It is the policy of the Office not to withhold approval until the validation process has been completed. We acknowledge your commitment to cooperate with the agency to satisfactorily resolve any deficiencies that may be identified during the validation process.

Sincerely yours,

/S/

Gary Buehler 8/18/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

FINAL PRINTED LABELING(S)

fougera®

℞ only

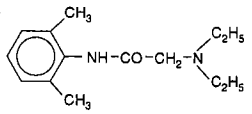
LIDOCAINE and PRILOCAINE CREAM, 2.5%/2.5%

NOT FOR OPHTHALMIC USE **FOR EXTERNAL USE ONLY**

DESCRIPTION

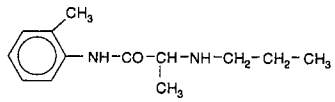
Lidocaine and prilocaine cream, 2.5%/2.5% is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals. It is packaged in 30 gram tubes.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4, and has the following structure:



$C_{14}H_{22}N_2O$ M.W. 234.3

Prilocaine is chemically designated as propanamide, *N*-(2-methylphenyl)-2-(propylamino), has an octanol:water partition ratio of 25 at pH 7.4, and has the following structure:



$C_{13}H_{20}N_2O$ M.W. 220.3

Each gram of lidocaine and prilocaine cream, 2.5%/2.5% contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carbomer 934 (as a thickening agent), sodium hydroxide to adjust to a pH approximating 9, and purified water. Lidocaine and prilocaine cream, 2.5%/2.5% contains no preservative, however it passes the USP antimicrobial effectiveness test due to the pH. The specific gravity of lidocaine and prilocaine cream, 2.5%/2.5% is approximately 1.

CLINICAL PHARMACOLOGY

Mechanism of Action: Lidocaine and prilocaine cream, 2.5%/2.5%, applied to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anesthetic agents. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

The onset, depth and duration of dermal analgesia on intact skin provided by lidocaine and prilocaine cream, 2.5%/2.5% depends primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, lidocaine and prilocaine cream, 2.5%/2.5% should be applied under an occlusive dressing for at least 1 hour. To provide dermal analgesia for clinical procedures such as split skin graft harvesting, lidocaine and prilocaine cream, 2.5%/2.5% should be applied under occlusive dressing for at least 2 hours. Satisfactory dermal analgesia is achieved 1 hour after application, reaches maximum at 2 to 3 hours, and persists for 1 to 2 hours after removal. Absorption from the genital mucosa is more rapid and onset time is shorter (5 to 10 minutes) than after application to intact skin. After a 5 to 10 minute application of lidocaine and prilocaine cream, 2.5%/2.5% to female genital mucosa, the average duration of effective analgesia to an argon laser stimulus (which produced a sharp, pricking pain) was 15 to 20 minutes (individual variations in the range of 5 to 45 minutes).

Dermal application of lidocaine and prilocaine cream, 2.5%/2.5% may cause a transient, local blanching followed by a transient, local redness or erythema.

Pharmacokinetics: Lidocaine and prilocaine cream, 2.5%/2.5% is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. In this eutectic mixture, both anesthetics are liquid at room temperature (see DESCRIPTION) and the penetration and subsequent systemic absorption of both prilocaine and lidocaine are enhanced over that which would be seen if each component in crystalline form was applied separately as a 2.5% topical cream.

Absorption-The amount of lidocaine and prilocaine systemically absorbed from lidocaine and prilocaine cream, 2.5%/2.5% is directly related to both the duration of application and to the area over which it is applied. In two pharmacokinetic studies, 60 g of lidocaine and prilocaine cream, 2.5%/2.5% (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm^2 of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the mg/kg (see ADVERSE REACTIONS). Very young patients, patients with glucose-6-phosphate dehydrogenase deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia (see Methemoglobinemia subsection of PRECAUTIONS).

Elimination- The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, ±3 SD, n=13). The elimination half-life of prilocaine is approximately 10 to 150 minutes (mean 70, ±48 SD, n=13). The systemic clearance is 18 to 64 mL/min/kg (mean 38, ±15 SD, n=13). During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients.

Pediatrics- Some pharmacokinetic (PK) data are available in infants (1 month to <2 years old) and children (2 to <12 years old). One PK study was conducted in 9 full-term neonates (mean age: 7 days and mean gestational age: 38.8 weeks). The study results show that neonates had comparable plasma lidocaine and prilocaine concentrations and blood methemoglobin concentrations as those found in previous pediatric PK studies and clinical trials. There was a tendency towards an increase in methemoglobin formation. However, due to assay limitations and very little amount of blood that could be collected from neonates, large variations in the above reported concentrations were found.

Special Populations- No specific PK studies were conducted. The half-life may be increased in cardiac or hepatic dysfunction. Prilocaine's half-life also may be increased in hepatic or renal dysfunction since both of these organs are involved in prilocaine metabolism.

CLINICAL STUDIES

Lidocaine and prilocaine cream, 2.5%/2.5% application in adults prior to IV cannulation or venipuncture was studied in 200 patients in four clinical studies in Europe. Application for at least 1 hour provided significantly more dermal analgesia than placebo cream or ethyl chloride. Lidocaine and prilocaine cream, 2.5%/2.5% was comparable to subcutaneous lidocaine, but was less efficacious than intradermal lidocaine. Most patients found lidocaine and prilocaine cream, 2.5%/2.5% treatment preferable to lidocaine infiltration or ethyl chloride spray.

Lidocaine and prilocaine cream, 2.5%/2.5% was compared with 0.5% lidocaine infiltration prior to skin graft harvesting in one open label study in 80 adult patients in England. Application of lidocaine and prilocaine cream, 2.5%/2.5% for 2 to 5 hours provided dermal analgesia comparable to lidocaine infiltration.

Lidocaine and prilocaine cream, 2.5%/2.5% application in children was studied in seven non-US studies (320 patients) and one US study (100 patients). In controlled studies, application of lidocaine and prilocaine cream, 2.5%/2.5% for at least 1 hour with or without presurgical medication prior to needle insertion provided significantly more pain reduction than placebo. In children under the age of seven years, lidocaine and prilocaine cream, 2.5%/2.5% was less effective than in older children or adults.

Lidocaine and prilocaine cream, 2.5%/2.5% was compared with placebo in the laser treatment of facial port-wine stains in 72 pediatric patients (ages 5-16). Lidocaine and prilocaine cream, 2.5%/2.5% was effective in providing pain relief during laser treatment.

Lidocaine and prilocaine cream, 2.5%/2.5% alone was compared to lidocaine and prilocaine cream, 2.5%/2.5% followed by lidocaine infiltration and lidocaine infiltration alone prior to cryotherapy for the removal of male genital warts. The data from 121 patients demonstrated that lidocaine and prilocaine cream, 2.5%/2.5% was not effective as a sole anesthetic agent in managing the pain from the surgical procedure. The administration of lidocaine and prilocaine cream, 2.5%/2.5% prior to lidocaine infiltration provided significant relief of discomfort associated with local anesthetic infiltration and thus was effective in the overall reduction of pain from the procedure only when used in conjunction with local anesthetic infiltration of lidocaine.

Lidocaine and prilocaine cream, 2.5%/2.5% was studied in 105 full term neonates (gestational age: 37 weeks) for blood drawing and circumcision procedures. When considering the use of lidocaine and prilocaine cream, 2.5%/2.5% in neonates, the primary concerns are the systemic absorption of the active ingredients and the subsequent formation of methemoglobin. In clinical studies performed in neonates, the plasma levels of lidocaine, prilocaine, and methemoglobin were not reported in a range expected to cause clinical symptoms.

Local dermal effects associated with lidocaine and prilocaine cream, 2.5%/2.5% application in these studies on intact skin included paleness, redness and edema and were transient in nature (see ADVERSE REACTIONS).

The application of lidocaine and prilocaine cream, 2.5%/2.5% on genital mucous membranes for minor, superficial surgical procedures (eg, removal of condylomata acuminata) was studied in 80 patients in a placebo-controlled clinical trial (60 patients received lidocaine and prilocaine cream, 2.5%/2.5% and 20 patients received placebo). Lidocaine and prilocaine cream, 2.5%/2.5% (5 to 10 g) applied between 1 and 75 minutes before surgery, with a median time of 15 minutes, provided effective local anesthesia for minor superficial surgical procedures. The greatest extent of analgesia, as measured by VAS pain scores, was attained after 5 to 15 minutes. The application of lidocaine and prilocaine cream, 2.5%/2.5% to genital mucous membranes as pretreatment for local anesthetic infiltration was studied in a double-blind, placebo-controlled study in 44 female patients (21 patients received lidocaine and prilocaine cream, 2.5%/2.5% and 23 patients received placebo) scheduled for infiltration prior to a surgical procedure of the external vulva or genital mucosa. Lidocaine and prilocaine cream, 2.5%/2.5% applied to the genital mucous membranes for 5 to 10 minutes resulted in adequate topical anesthesia for local anesthetic injection.

Individualization of Dose: The dose of lidocaine and prilocaine cream, 2.5%/2.5% which provides effective analgesia depends on the duration of the application over the treated area.

of lidocaine and prilocaine

CLINICAL PHARMACOLOGY

Mechanism of Action: Lidocaine and prilocaine cream, 2.5%/2.5%, applied to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anesthetic agents. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

The onset, depth and duration of dermal analgesia on intact skin provided by lidocaine and prilocaine cream, 2.5%/2.5% depends primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, lidocaine and prilocaine cream, 2.5%/2.5% should be applied under an occlusive dressing for at least 1 hour. To provide dermal analgesia for clinical procedures such as split skin graft harvesting, lidocaine and prilocaine cream, 2.5%/2.5% should be applied under occlusive dressing for at least 2 hours. Satisfactory dermal analgesia is achieved 1 hour after application, reaches maximum at 2 to 3 hours, and persists for 1 to 2 hours after removal. Absorption from the genital mucosa is more rapid and onset time is shorter (5 to 10 minutes) than after application to intact skin. After a 5 to 10 minute application of lidocaine and prilocaine cream, 2.5%/2.5% to female genital mucosa, the average duration of effective analgesia to an argon laser stimulus (which produced a sharp, pricking pain) was 15 to 20 minutes (individual variations in the range of 5 to 45 minutes).

Dermal application of lidocaine and prilocaine cream, 2.5%/2.5% may cause a transient, local blanching followed by a transient, local redness or erythema.

Pharmacokinetics: Lidocaine and prilocaine cream, 2.5%/2.5% is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. In this eutectic mixture, both anesthetics are liquid at room temperature (see DESCRIPTION) and the penetration and subsequent systemic absorption of both prilocaine and lidocaine are enhanced over that which would be seen if each component in crystalline form was applied separately as a 2.5% topical cream.

Absorption-The amount of lidocaine and prilocaine systemically absorbed from lidocaine and prilocaine cream, 2.5%/2.5% is directly related to both the duration of application and to the area over which it is applied. In two pharmacokinetic studies, 60 g of lidocaine and prilocaine cream, 2.5%/2.5% (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm^2 of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the subjects had the occlusive dressing and residual cream removed after 3 hours, while the remainder left the dressing in place for 24 hours. The results from these studies are summarized below.

TABLE 1
Absorption of Lidocaine and Prilocaine from Lidocaine and Prilocaine Cream, 2.5%/2.5%: Normal Volunteers (N=16)

Lidocaine and Prilocaine Cream, 2.5%/2.5% (g)	Area (cm^2)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	Cmax (mcg/ml)	Tmax (hr)
60	400	3	lidocaine 1500	54	0.12	4
			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

* Maximum recommended duration of exposure is 4 hours.

When 60 g of lidocaine and prilocaine cream, 2.5%/2.5% was applied over 400 cm^2 for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. In a pharmacokinetic study, lidocaine and prilocaine cream, 2.5%/2.5% was applied to penile skin in 20 adult male patients in doses ranging from 0.5 g to 3.3 g for 15 minutes. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream, 2.5%/2.5% application in this study were consistently low (2.5-16 ng/mL for lidocaine and 2.5-7 ng/mL for prilocaine). The application of lidocaine and prilocaine cream, 2.5%/2.5% to broken or inflamed skin, or to 2,000 cm^2 or more of skin where more of both anesthetics are absorbed, could result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response.

The absorption of lidocaine and prilocaine cream, 2.5%/2.5% applied to genital mucous membranes was studied in two open-label clinical trials. Twenty-nine patients received 10 g of lidocaine and prilocaine cream, 2.5%/2.5% applied for 10 to 60 minutes in the vaginal fornices. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream, 2.5%/2.5% application in these studies ranged from 148 to 641 ng/mL for lidocaine and 40 to 346 ng/mL for prilocaine and time to reach maximum concentration (t_{max}) ranged from 21 to 125 minutes for lidocaine and from 21 to 95 minutes for prilocaine. These levels are well below the concentrations anticipated to give rise to systemic toxicity (approximately 5000 ng/mL for lidocaine and prilocaine).

Distribution- When each drug is administered intravenously, the steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5, ±0.3 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ±1.3 SD, n=13) for prilocaine. The larger distribution volume for prilocaine produces the lower plasma concentrations of prilocaine observed when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of lidocaine and prilocaine cream, 2.5%/2.5%, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mcg/mL of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

Metabolism- It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from

prilocaine cream, 2.5%/2.5% followed by lidocaine infiltration and lidocaine infiltration alone prior to cryotherapy for the removal of male genital warts. The data from 121 patients demonstrated that lidocaine and prilocaine cream, 2.5%/2.5% was not effective as a sole anesthetic agent in managing the pain from the surgical procedure. The administration of lidocaine and prilocaine cream, 2.5%/2.5% prior to lidocaine infiltration provided significant relief of discomfort associated with local anesthetic infiltration and thus was effective in the overall reduction of pain from the procedure only when used in conjunction with local anesthetic infiltration of lidocaine.

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Local dermal effects associated with lidocaine and prilocaine cream, 2.5%/2.5% application in these studies on intact skin included paleness, redness and edema and were transient in nature (see ADVERSE REACTIONS).

The application of lidocaine and prilocaine cream, 2.5%/2.5% on genital mucous membranes for minor, superficial surgical procedures (eg, removal of condylomata acuminata) was studied in 80 patients in a placebo-controlled clinical trial (60 patients received lidocaine and prilocaine cream, 2.5%/2.5% and 20 patients received placebo). Lidocaine and prilocaine cream, 2.5%/2.5% (5 to 10 g) applied between 1 and 75 minutes before surgery, with a median time of 15 minutes, provided effective local anesthesia for minor superficial surgical procedures. The greatest extent of analgesia, as measured by VAS pain scores, was attained after 5 to 15 minutes. The application of lidocaine and prilocaine cream, 2.5%/2.5% to genital mucous membranes as pretreatment for local anesthetic infiltration was studied in a double-blind, placebo-controlled study in 44 female patients (21 patients received lidocaine and prilocaine cream, 2.5%/2.5% and 23 patients received placebo) scheduled for infiltration prior to a surgical procedure of the external vulva or genital mucosa. Lidocaine and prilocaine cream, 2.5%/2.5% applied to the genital mucous membranes for 5 to 10 minutes resulted in adequate topical anesthesia for local anesthetic injection.

Individualization of Dose: The dose of lidocaine and prilocaine cream, 2.5%/2.5% which provides effective analgesia depends on the duration of the application over the treated area.

All pharmacokinetic and clinical studies employed a thick layer of lidocaine and prilocaine cream, 2.5%/2.5% (1-2 g/10 cm^2). The duration of application prior to venipuncture was 1 hour. The duration of application prior to taking split thickness skin grafts was 2 hours. Although a thinner application may be efficacious, such has not been studied and may result in less complete analgesia or a shorter duration of adequate analgesia.

The systemic absorption of lidocaine and prilocaine is a side effect of the desired local effect. The amount of drug absorbed depends on surface area and duration of application. The systemic blood levels depend on the amount absorbed and patient size (weight) and rate of systemic drug elimination. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels. The systemic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels which produce toxicity. Table 2 which follows gives maximum recommended doses, application areas and application times for infants and children.

TABLE 2
LIDOCAINE AND PRILOCAINE CREAM, 2.5%/2.5% MAXIMUM RECOMMENDED DOSE, APPLICATION AREA, AND APPLICATION TIME BY AGE AND WEIGHT*
For Infants and Children
Based on Application to Intact Skin

Age and Body Weight Requirements	Maximum total Dose of Lidocaine and Prilocaine Cream, 2.5%/2.5%	Maximum Application Area**	Maximum Application Time
0 up to 3 months or < 5 kg	1g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream, 2.5%/2.5% should be restricted to that which corresponds to the patient's **weight**.

* These are broad guidelines for avoiding systemic toxicity in applying lidocaine and prilocaine cream, 2.5%/2.5% to patients with normal intact skin and with normal renal and hepatic function.

** For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults:

The estimated mean (±SD) absorption of lidocaine is 0.045 (±0.016) mg/cm^2/hr.
The estimated mean (±SD) absorption of prilocaine is 0.077 (±0.036) mg/cm^2/hr.

An IV antiarrhythmic dose of lidocaine is 1 mg/kg (70 mg/70 kg) and gives a blood level of about 1 mcg/mL. Toxicity would be expected at blood levels above 5 mcg/mL. Smaller areas of treatment are recommended in a debilitated patient, a small child or a patient with impaired elimination. Decreasing the duration of application is likely to decrease the analgesic effect.

INDICATIONS AND USAGE

Lidocaine and prilocaine cream, 2.5%/2.5% (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:

- normal intact skin for local analgesia.
- genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.

Lidocaine and prilocaine cream, 2.5%/2.5% is not recommended in any clinical situation in which penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies (see WARNINGS).

CONTRAINDICATIONS

2.5%/2.5% is contraindicated in patients with a known

Absorption of Lidocaine and Prilocaine from Lidocaine and Prilocaine Cream, 2.5%/2.5%: Normal Volunteers (N=16)

Lidocaine and Prilocaine Cream, 2.5%/2.5% (g)	Area (cm^2)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	Cmax (mcg/ml)	Tmax (hr)
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			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

* Maximum recommended duration of exposure is 4 hours.

When 60 g of lidocaine and prilocaine cream, 2.5%/2.5% was applied over 400 cm^2 for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. In a pharmacokinetic study, lidocaine and prilocaine cream, 2.5%/2.5% was applied to penile skin in 20 adult male patients in doses ranging from 0.5 g to 3.3 g for 15 minutes. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream, 2.5%/2.5% application in this study were consistently low (2.5-16 ng/mL for lidocaine and 2.5-7 ng/mL for prilocaine). The application of lidocaine and prilocaine cream, 2.5%/2.5% to broken or inflamed skin, or to 2,000 cm^2 or more of skin where more of both anesthetics are absorbed, could result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response.

The absorption of lidocaine and prilocaine cream, 2.5%/2.5% applied to genital mucous membranes was studied in two open-label clinical trials. Twenty-nine patients received 10 g of lidocaine and prilocaine cream, 2.5%/2.5% applied for 10 to 60 minutes in the vaginal fornices. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream, 2.5%/2.5% application in these studies ranged from 148 to 641 ng/mL for lidocaine and 40 to 346 ng/mL for prilocaine and time to reach maximum concentration (t_{max}) ranged from 21 to 125 minutes for lidocaine and from 21 to 95 minutes for prilocaine. These levels are well below the concentrations anticipated to give rise to systemic toxicity (approximately 5000 ng/mL for lidocaine and prilocaine).

Distribution- When each drug is administered intravenously, the steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5, ±0.3 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ±1.3 SD, n=13) for prilocaine. The larger distribution volume for prilocaine produces the lower plasma concentrations of prilocaine observed when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of lidocaine and prilocaine cream, 2.5%/2.5%, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mcg/mL of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

Metabolism- It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including *ortho*-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases. The *ortho*-toluidine metabolite has been shown to be carcinogenic in several animal models (see Carcinogenesis subsection of PRECAUTIONS). In addition, *ortho*-toluidine can produce methemoglobinemia following systemic doses of prilocaine approximating 8

result in less complete analgesia or a shorter duration of adequate analgesia.

The systemic absorption of lidocaine and prilocaine is a side effect of the desired local effect. The amount of drug absorbed depends on surface area and duration of application. The systemic blood levels depend on the amount absorbed and patient size (weight) and rate of systemic drug elimination. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels. The systemic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels which produce toxicity. Table 2 which follows gives maximum recommended doses, application areas and application times for infants and children.

TABLE 2
LIDOCAINE AND PRILOCAINE CREAM, 2.5%/2.5% MAXIMUM RECOMMENDED DOSE, APPLICATION AREA, AND APPLICATION TIME BY AGE AND WEIGHT*
For Infants and Children
Based on Application to Intact Skin

Age and Body Weight Requirements	Maximum total Dose of Lidocaine and Prilocaine Cream, 2.5%/2.5%	Maximum Application Area**	Maximum Application Time
0 up to 3 months or < 5 kg	1g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream, 2.5%/2.5% should be restricted to that which corresponds to the patient's weight.

* These are broad guidelines for avoiding systemic toxicity in applying lidocaine and prilocaine cream, 2.5%/2.5% to patients with normal intact skin and with normal renal and hepatic function.

** For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults:

The estimated mean (±SD) absorption of lidocaine is 0.045 (±0.016) mg/cm^2/hr.
The estimated mean (±SD) absorption of prilocaine is 0.077 (±0.036) mg/cm^2/hr.

An IV antiarrhythmic dose of lidocaine is 1 mg/kg (70 mg/70 kg) and gives a blood level of about 1 mcg/mL. Toxicity would be expected at blood levels above 5 mcg/mL. Smaller areas of treatment are recommended in a debilitated patient, a small child or a patient with impaired elimination. Decreasing the duration of application is likely to decrease the analgesic effect.

INDICATIONS AND USAGE

Lidocaine and prilocaine cream, 2.5%/2.5% (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:
- **normal intact skin** for local analgesia.
- **genital mucous membranes** for superficial minor surgery and as pretreatment for infiltration anesthesia.

Lidocaine and prilocaine cream, 2.5%/2.5% is not recommended in any clinical situation in which penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies (see WARNINGS).

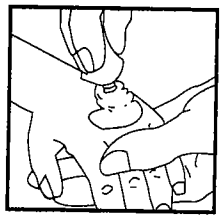
CONTRAINDICATIONS

Lidocaine and prilocaine cream, 2.5%/2.5% is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

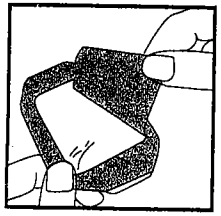
Remove this portion before dispensing

INSTRUCTIONS FOR APPLICATION

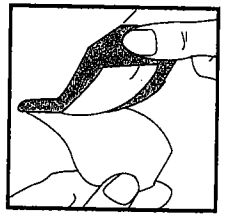
Lidocaine and Prilocaine Cream, 2.5%/2.5%



1. In adults, apply 2.5 g of cream per 20 to 25 cm^2 (approx. 2 in. by 2 in.) of skin in a thick layer at the site of the procedure. For pediatric patients, apply ONLY as prescribed by your physician. If your child is below the age of 3 months or small for their age, please inform your doctor before applying lidocaine and prilocaine cream, 2.5%/2.5%, which can be harmful, if applied over too much skin at one time in young children. If your child becomes very dizzy, excessively sleepy, or develops duskiness of the face or lips after applying lidocaine and prilocaine cream, 2.5%/2.5%, remove the cream and contact your physician at once.



2. Take any occlusive dressing (not included in this package).



3. Peel the paper liner from the dressing. (Instructions continued on reverse side.)

WARNINGS

Application of lidocaine and prilocaine cream, 2.5%/2.5% to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

Studies in laboratory animals (guinea pigs) have shown that lidocaine and prilocaine cream, 2.5%/2.5% has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to lidocaine and prilocaine cream, 2.5%/2.5% in the external auditory canal only, showed no abnormality. Lidocaine and prilocaine cream, 2.5%/2.5% should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Methemoglobinemia: Lidocaine and prilocaine cream, 2.5%/2.5% should not be used in those rare patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.

Very young patients or patients with glucose-6-phosphate dehydrogenase deficiencies are more susceptible to methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine, are also at greater risk for developing methemoglobinemia.

There have been reports of significant methemoglobinemia (20-30%) in infants and children following excessive applications of lidocaine and prilocaine cream, 2.5%/2.5%. These cases involved the use of large doses, larger than recommended areas of application, or infants under the age of 3 months who did not have fully mature enzyme systems. In addition, a few of these cases involved the concomitant administration of methemoglobin-inducing agents. Most patients recovered spontaneously after removal of the cream. Treatment with IV methylene blue may be effective if required.

Physicians are cautioned to make sure that parents or other caregivers understand the need for careful application of lidocaine and prilocaine cream, 2.5%/2.5%, to ensure that the doses and areas of application recommended in Table 2 are not exceeded (especially in children under the age of 3 months) and to limit the period of application to the minimum required to achieve the desired anesthesia.

Neonates and infants up to 3 months of age should be monitored for Met-Hb levels before, during, and after the application of lidocaine and prilocaine cream, 2.5%/2.5%, provided the test results can be obtained quickly.

PRECAUTIONS

General: Repeated doses of lidocaine and prilocaine cream, 2.5%/2.5% may increase blood levels of lidocaine and prilocaine. Lidocaine and prilocaine cream, 2.5%/2.5% should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients.

Lidocaine and prilocaine cream, 2.5%/2.5% coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of lidocaine and prilocaine cream, 2.5%/2.5% in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine, however, lidocaine and prilocaine cream, 2.5%/2.5% should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Lidocaine and prilocaine have been shown to inhibit viral and bacterial growth. The effect of lidocaine and prilocaine cream, 2.5%/2.5% on **intradermal** injections of **live** vaccines has not been determined.

Information for Patients: When lidocaine and prilocaine cream, 2.5%/2.5% is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Drug Interactions: Lidocaine and prilocaine cream, 2.5%/2.5% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis- Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of lidocaine and prilocaine cream, 2.5%/2.5% to 400 cm² for 3 hours to a small person (50 kg). The typical application of lidocaine and prilocaine cream, 2.5%/2.5% for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to 14,400 mg/m²; 60 to 960 times SDA) and rats (900 to 4,800 mg/m²; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m²; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of lidocaine and prilocaine cream, 2.5%/2.5% are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of lidocaine and prilocaine cream, 2.5%/2.5%. Consideration should be given for those elderly patients who have enhanced sensitivity to systemic absorption. (See PRECAUTIONS.)

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with lidocaine and prilocaine cream, 2.5%/2.5% on intact skin, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. Rare cases of discrete purpuric or petechial reactions at the application site have been reported. Rare cases of hyperpigmentation following the use of lidocaine and prilocaine cream, 2.5%/2.5% have been reported. The relationship to lidocaine and prilocaine cream, 2.5%/2.5% or the underlying procedure has not been established. In clinical studies on intact skin involving over 1,300 lidocaine and prilocaine cream, 2.5%/2.5%-treated subjects, one or more such local reactions were noted in 56% of patients, and were generally mild and transient, resolving spontaneously within 1 or 2 hours. There were no serious reactions which were ascribed to lidocaine and prilocaine cream, 2.5%/2.5%.

Two recent reports describe blistering on the foreskin in neonates about to undergo circumcision. Both neonates received 1 g of lidocaine and prilocaine cream, 2.5%/2.5%.

In patients treated with lidocaine and prilocaine cream, 2.5%/2.5% on intact skin, local effects observed in the trials included: paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, itching 2% and rash, less than 1%.

In clinical studies on genital mucous membranes involving 378 lidocaine and prilocaine cream, 2.5%/2.5%-treated patients, one or more application site reactions, usually mild and transient, were noted in 41% of patients. The most common application site reactions were redness (21%), burning sensation (17%) and edema (10%).

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of lidocaine and prilocaine cream, 2.5%/2.5% are unlikely due to the small dose absorbed (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Systemic adverse effects of lidocaine and/or prilocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Peak blood levels following a 60 g application to 400 cm² of intact skin for 3 hours are 0.05 to 0.16 mcg/mL for lidocaine and 0.02 to 0.10 mcg/mL for prilocaine. Toxic levels of lidocaine (>5 mcg/mL) and/or prilocaine (>6 mcg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

DOSAGE AND ADMINISTRATION

Adult Patients-Intact Skin

A thick layer of lidocaine and prilocaine cream, 2.5%/2.5% is applied to intact skin and covered with an occlusive dressing.

Minor Dermal Procedures: For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of lidocaine and prilocaine cream, 2.5%/2.5% over 20 to 25 cm² of skin surface for at least 1 hour. In controlled clinical trials using lidocaine and prilocaine cream, 2.5%/2.5%, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of lidocaine and prilocaine cream, 2.5%/2.5% per 10 cm² of skin and allow to remain in contact with the skin for at least 2 hours.

Adult Male Genital Skin: As an adjunct prior to local anesthetic infiltration, apply a thick layer of lidocaine and prilocaine cream, 2.5%/2.5% (1 g/10 cm²) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of lidocaine and prilocaine cream, 2.5%/2.5%.

Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. The amount of lidocaine and prilocaine absorbed during the period of application can be estimated from the information in Table 2, ** footnote, in Individualization of Dose.

Adult Female Patients-Genital Mucous Membranes

For minor procedures on the female external genitalia, such as removal of condylomata acuminata, as well as for use as pretreatment for anesthetic infiltration, apply a thick layer (5-10 grams) of lidocaine and prilocaine cream, 2.5%/2.5% for 5 to 10 minutes.

Occlusion is not necessary for absorption, but may be helpful to keep the cream in place

sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Lidocaine and prilocaine have been shown to inhibit viral and bacterial growth. The effect of lidocaine and prilocaine cream, 2.5%/2.5% on **intradermal** injections of live vaccines has not been determined.

Information for Patients: When lidocaine and prilocaine cream, 2.5%/2.5% is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Drug Interactions: Lidocaine and prilocaine cream, 2.5%/2.5% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis- Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of lidocaine and prilocaine cream, 2.5%/2.5% to 400 cm^2 for 3 hours to a small person (50 kg). The typical application of lidocaine and prilocaine cream, 2.5%/2.5% for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to 14,400 mg/m^2; 60 to 960 times SDA) and rats (900 to 4,800 mg/m^2; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m^2; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 times SDA. The animal studies were conducted at 150 to 2,400 mg/kg in mice and at 150 to 800 mg/kg in rats. The dosages have been converted to mg/m^2 for the SDA calculations above.

Mutagenesis- The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. There was no indication in these three tests of any mutagenic effects.

Ortho-toluidine, a metabolite of prilocaine, (0.5 mcg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho*-toluidine (300 mg/kg orally; 300 times SDA) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests on *ortho*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation and with single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility- See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine and prilocaine cream, 2.5%/2.5% should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should lidocaine and prilocaine cream, 2.5%/2.5% be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when lidocaine and prilocaine cream, 2.5%/2.5% is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of lidocaine and prilocaine cream, 2.5%/2.5% in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

Lidocaine and prilocaine cream, 2.5%/2.5% should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

When using lidocaine and prilocaine cream, 2.5%/2.5% in young children, especially infants under the age of 3 months, care must be taken to insure that the caregiver understands the need to limit the dose and area of application, and to prevent accidental ingestion (see DOSAGE AND ADMINISTRATION and Methemoglobinemia).

In neonates (minimum gestation age: 37 weeks) and children weighing less than 20 kg, the area and duration of application should be limited (see TABLE 2 in Individualization of Dose).

Geriatric Use

Of the total number of patients in clinical studies of lidocaine and prilocaine cream, 2.5%/2.5%, 180 were age 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other

to 0.16 mcg/mL for lidocaine and 0.02 to 0.10 mcg/mL for prilocaine. Toxic levels of lidocaine (>5 mcg/mL) and/or prilocaine (>6 mcg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

DOSAGE AND ADMINISTRATION

Adult Patients-Intact Skin

A thick layer of lidocaine and prilocaine cream, 2.5%/2.5% is applied to intact skin and covered with an occlusive dressing.

Minor Dermal Procedures: For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of lidocaine and prilocaine cream, 2.5%/2.5% over 20 to 25 cm^2 of skin surface for at least 1 hour. In controlled clinical trials using lidocaine and prilocaine cream, 2.5%/2.5%, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of lidocaine and prilocaine cream, 2.5%/2.5% per 10 cm^2 of skin and allow to remain in contact with the skin for at least 2 hours.

Adult Male Genital Skin: As an adjunct prior to local anesthetic infiltration, apply a thick layer of lidocaine and prilocaine cream, 2.5%/2.5% (1 g/10 cm^2) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of lidocaine and prilocaine cream, 2.5%/2.5%.

Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. The amount of lidocaine and prilocaine absorbed during the period of application can be estimated from the information in Table 2, ** footnote, in Individualization of Dose.

Adult Female Patients-Genital Mucous Membranes

For minor procedures on the female external genitalia, such as removal of condylomata acuminata, as well as for use as pretreatment for anesthetic infiltration, apply a thick layer (5-10 grams) of lidocaine and prilocaine cream, 2.5%/2.5% for 5 to 10 minutes.

Occlusion is not necessary for absorption, but may be helpful to keep the cream in place. Patients should be lying down during the lidocaine and prilocaine cream, 2.5%/2.5% application, especially if no occlusion is used. The procedure or the local anesthetic infiltration should be performed immediately after the removal of lidocaine and prilocaine cream, 2.5%/2.5%.

Pediatric Patients-Intact Skin

The following are the maximum recommended doses, application areas and application times for lidocaine and prilocaine cream, 2.5%/2.5% based on a child's age and weight:

Age and Body Weight Requirements	Maximum total Dose of Lidocaine and Prilocaine Cream, 2.5%/2.5%	Maximum Application Area	Maximum Application Time
0 up to 3 months or < 5 kg	1g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream, 2.5%/2.5% should be restricted to that which corresponds to the patient's **weight.**

Practitioners should carefully instruct caregivers to avoid application of excessive amounts of lidocaine and prilocaine cream, 2.5%/2.5% (see PRECAUTIONS).

When applying lidocaine and prilocaine cream, 2.5%/2.5% to the skin of young children, care must be taken to maintain careful observation of the child to prevent accidental ingestion of lidocaine and prilocaine cream, 2.5%/2.5% or the occlusive dressing. A secondary protective covering to prevent inadvertent disruption of the application site may be useful.

Lidocaine and prilocaine cream, 2.5%/2.5% should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).

When lidocaine and prilocaine cream, 2.5%/2.5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered (see Individualization of Dose). The amount absorbed in the case of lidocaine and prilocaine cream, 2.5%/2.5% is determined by the area over which it is applied and the duration of application under occlusion (see Table 2, ** footnote, in Individualization of Dose).

Although the incidence of systemic adverse reactions with lidocaine and prilocaine cream, 2.5%/2.5% is very low, caution should be exercised, particularly when applying it over large areas and leaving it on for longer than 2 hours. The incidence of systemic adverse reactions can be expected to be directly proportional to the area and time of exposure (see Individualization of Dose).

HOW SUPPLIED

Lidocaine and prilocaine cream, 2.5%/2.5% is available as
NDC 0168-0357-30 30 gram tube

NOT FOR OPHTHALMIC USE.

KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.

WARNING: Keep out of reach of children.

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

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a division of Altana Inc.
Melville, New York 11747
I2357
R4/03
#42

AUG 18 2003
APPROVED

Mutagenesis- The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. There was no indication in these three tests of any mutagenic effects.

Ortho-toluidine, a metabolite of prilocaine, (0.5 mcg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho*-toluidine (300 mg/kg orally; 300 times SDA) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests on *ortho*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation and with single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility- See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine and prilocaine cream, 2.5%/2.5% should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should lidocaine and prilocaine cream, 2.5%/2.5% be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when lidocaine and prilocaine cream, 2.5%/2.5% is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of lidocaine and prilocaine cream, 2.5%/2.5% in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

Lidocaine and prilocaine cream, 2.5%/2.5% should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

When using lidocaine and prilocaine cream, 2.5%/2.5% in young children, especially infants under the age of 3 months, care must be taken to insure that the caregiver understands the need to limit the dose and area of application, and to prevent accidental ingestion (see DOSAGE AND ADMINISTRATION and Methemoglobinemia).

In neonates (minimum gestation age: 37 weeks) and children weighing less than 20 kg, the area and duration of application should be limited (see TABLE 2 in Individualization of Dose).

Geriatric Use

Of the total number of patients in clinical studies of lidocaine and prilocaine cream, 2.5%/2.5%, 180 were age 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other cream, 2.5%/2.5%.

Pediatric Patients-Intact Skin

The following are the maximum recommended doses, application areas and application times for lidocaine and prilocaine cream, 2.5%/2.5% based on a child's age and weight:

Age and Body Weight Requirements	Maximum total Dose of Lidocaine and Prilocaine Cream, 2.5%/2.5%	Maximum Application Area	Maximum Application Time
0 up to 3 months or < 5 kg	1g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream, 2.5%/2.5% should be restricted to that which corresponds to the patient's **weight.**

Practitioners should carefully instruct caregivers to avoid application of excessive amounts of lidocaine and prilocaine cream, 2.5%/2.5% (see PRECAUTIONS).

When applying lidocaine and prilocaine cream, 2.5%/2.5% to the skin of young children, care must be taken to maintain careful observation of the child to prevent accidental ingestion of lidocaine and prilocaine cream, 2.5%/2.5% or the occlusive dressing. A secondary protective covering to prevent inadvertent disruption of the application site may be useful.

Lidocaine and prilocaine cream, 2.5%/2.5% should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).

When lidocaine and prilocaine cream, 2.5%/2.5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered (see Individualization of Dose). The amount absorbed in the case of lidocaine and prilocaine cream, 2.5%/2.5% is determined by the area over which it is applied and the duration of application under occlusion (see Table 2, ** footnote, in Individualization of Dose).

Although the incidence of systemic adverse reactions with lidocaine and prilocaine cream, 2.5%/2.5% is very low, caution should be exercised, particularly when applying it over large areas and leaving it on for longer than 2 hours. The incidence of systemic adverse reactions can be expected to be directly proportional to the area and time of exposure (see Individualization of Dose).

HOW SUPPLIED

Lidocaine and prilocaine cream, 2.5%/2.5% is available as
NDC 0168-0357-30 30 gram tube

NOT FOR OPHTHALMIC USE.

KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.

WARNING: Keep out of reach of children.

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

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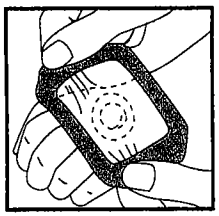
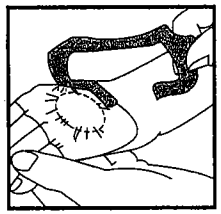
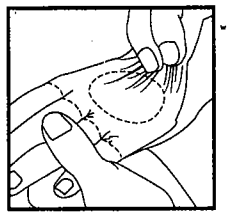


4. Cover the lidocaine and prilocaine cream, 2.5%/2.5% so that you get a thick layer underneath. Do not spread out the cream. Smooth down the dressing edges carefully and ensure it is secure to avoid leakage. (This is especially important when the patient is a child.)



5. The time of application can be marked directly on the occulsive dressing. Lidocaine and prilocaine cream, 2.5%/2.5% must be applied at least 1 hour before the start of a routine procedure and for 2 hours before the start of a painful procedure.



6. Remove the occlusive dressing, wipe off the lidocaine and prilocaine cream, 2.5%/2.5%, clean the entire area with an antiseptic solution and prepare the patient for the procedure. The duration of effective skin anesthesia will be at least 1 hour after removal of the occlusive dressing.

PRECAUTIONS

1. Do not apply near eyes or on open wounds.

2. Keep out of reach of children.

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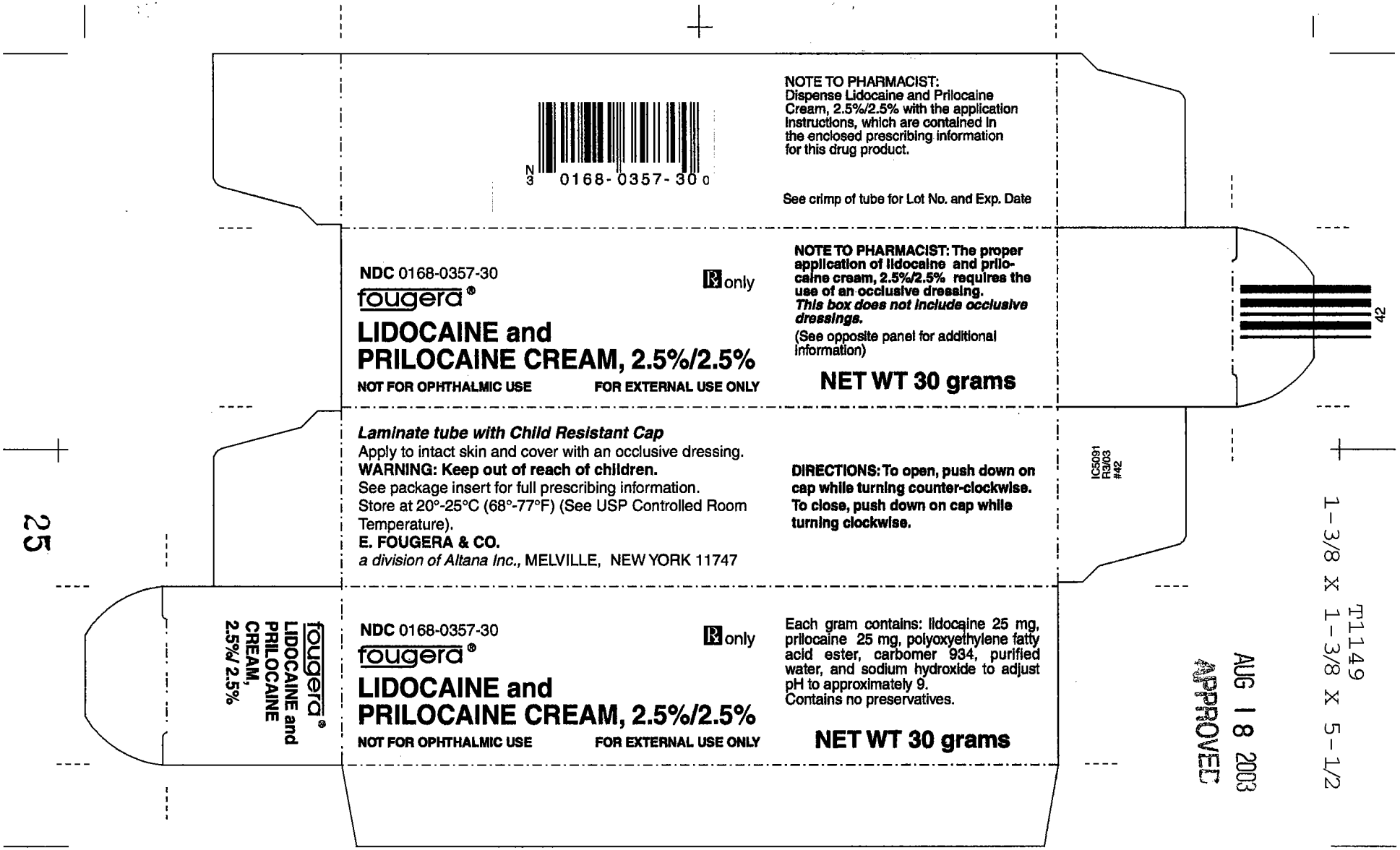


Item# IC5091
Die Size: 1.375" x 1.375" x 5.50"
SSC-2
Pharmacode: #42
Colors: Black, Process Yellow

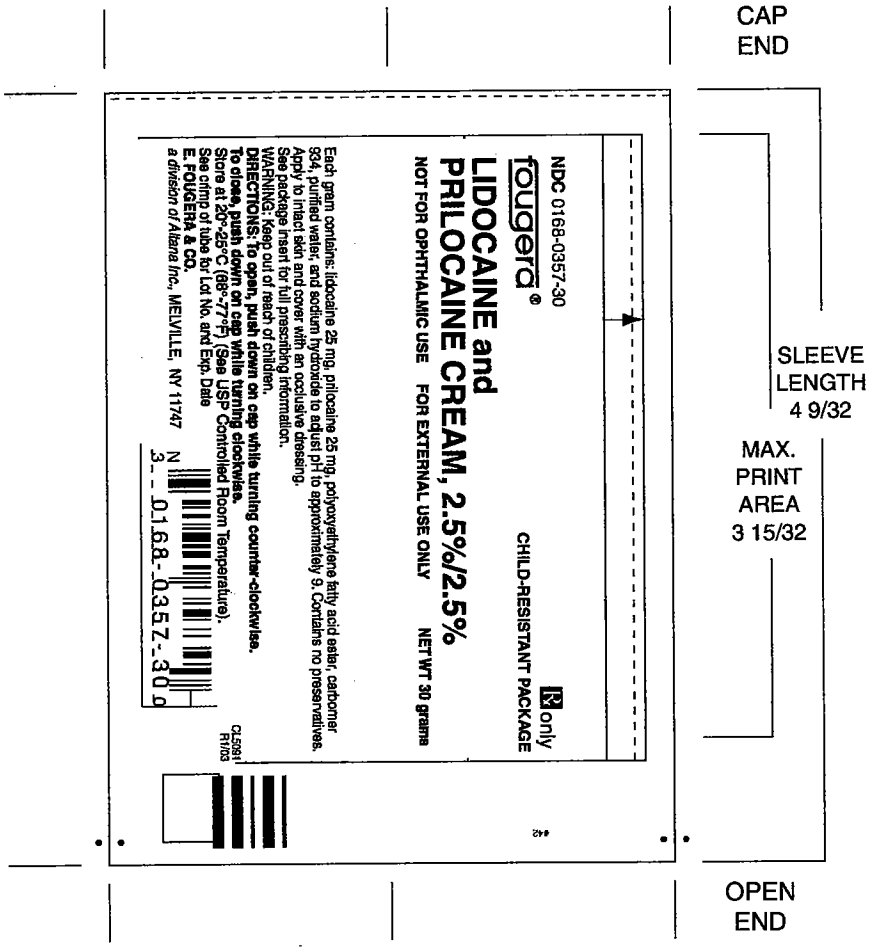
Revise per FDA letter, change Rdate
Sales edit

AA-3/11/02
AA-3/18/03

TEMPLATE FOR GLAMINATE TUBE
SUPPLIED BY AMERICAN NATIONAL CAN GRAPHICS

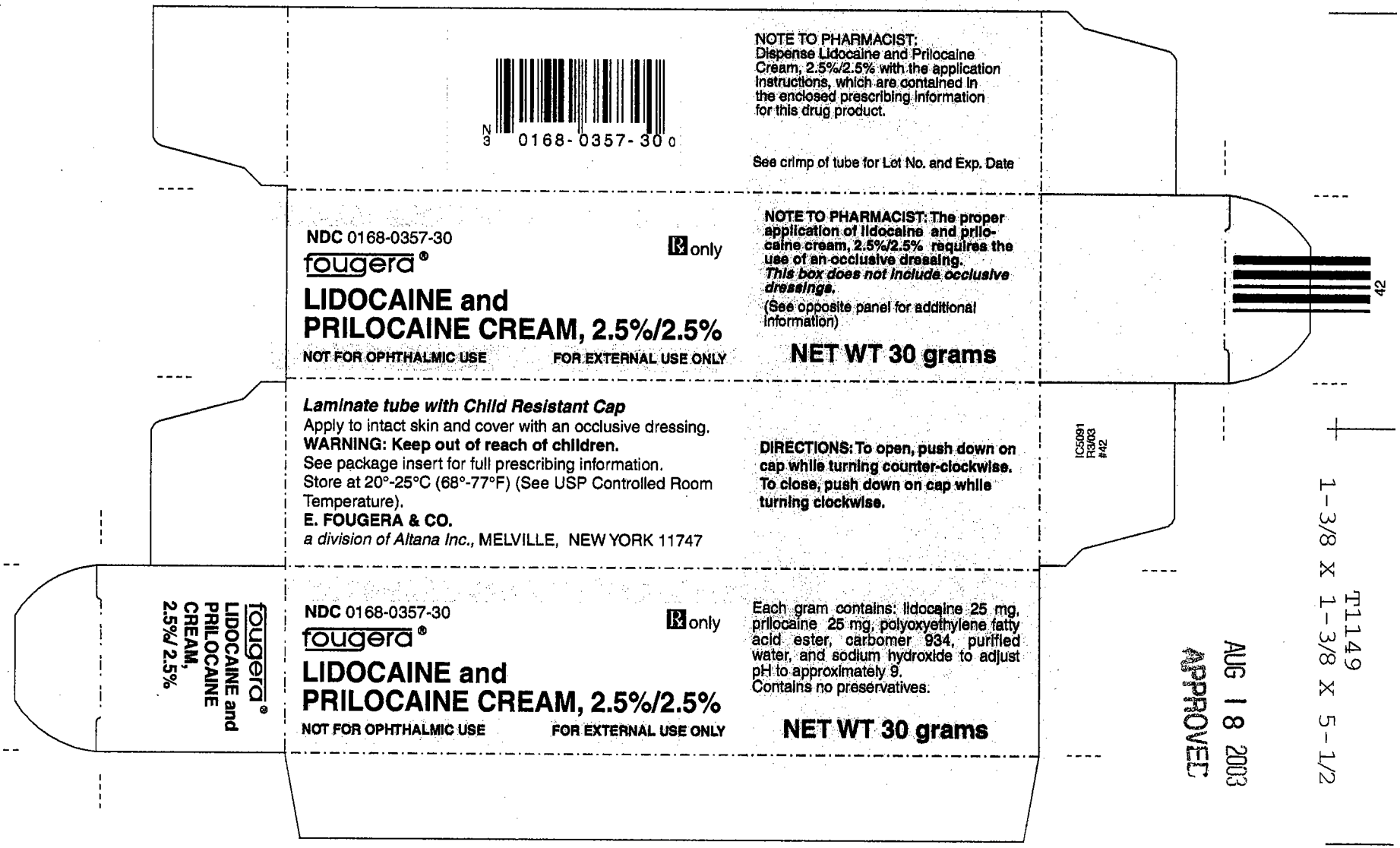
DATE: 2/19/99	TUBE SIZE: 1 X 4 1/4
CUSTOMER: ALTANA	EE SIZE: 5/16 X 3/8
PRODUCT: N/A	

AUG 18 2003 APPROVED



Item# CL5091
Colors Black, Process Yellow

WARNING: THIS IS AN OVERLAY. DO NOT INCLUDE DIRECTLY ON YOUR ARTWORK.



Item# IC5091
Die Size: 1.375" x 1.375" x 5.50"
SSC-2
Pharmacode: #42
Colors: Black, Process Yellow

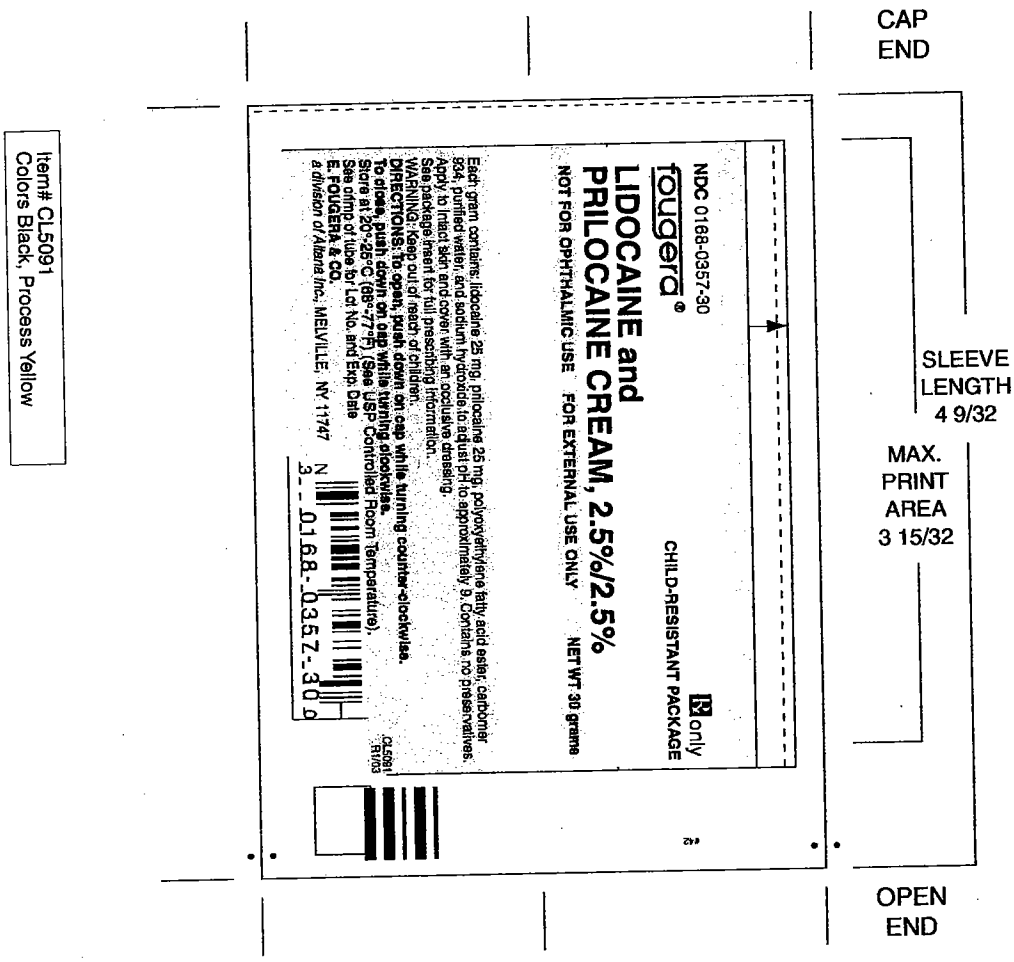
Revise per FDA letter, change Rdate
Sales edit

AA-3/11/02
AA-3/18/03

TEMPLATE FOR GLAMINATE TUBE
SUPPLIED BY AMERICAN NATIONAL CAN GRAPHICS

DATE: 2/19/99	TUBE SIZE: 1 X 4 1/4
CUSTOMER: ALTANA	EE SIZE: 5/16 X 3/8
PRODUCT: N/A	

AUG 18 2003 APPROVED



WARNING: THIS IS AN OVERLAY. DO NOT INCLUDE DIRECTLY ON YOUR ARTWORK.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

CSO LABELING REVIEW(S)

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-453 Date of Submission: April 28, 2003

Applicant's Name: Altana Inc.

Established Name: Lidocaine and Prilocaine Cream, 2.5%/2.5%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 grams

Satisfactory in FPL as of 3/18/03 submission (vol. 2.1, Attachment II)

Carton Labeling: 1 x 30 gm

Satisfactory in FPL as of 3/18/03 submission (vol. 2.1, Attachment II)

Professional Package Insert Labeling:

Satisfactory in FPL as of **4/28/03** submission (vol. 2.1, Rev. 4/03, Attachment II)

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Emla® cream
- NDA Number: 19-941/S-015
- NDA Drug Name: Emla® cream
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: S-015/ January 27, 03
- 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
- Basis of Approval for the Carton Labeling: Side-by-side

Other Comments:

See FTR # 9 regarding "Instructions for Application".

FOR THE RECORD:

1. Review based on the labeling of EMLA Cream, NDA 19-941/S-015, approved January 27, 03. The labeling supplement S-014 has been superseded by S-015. S-015 provides for a change in the container-closure system.

2. Patent/ Exclusivities

   None

3. Storage Conditions:
   NDA -Store at controlled room temperature 15^0-30^0C (59^0 - 86^0F).
   ANDA - Store at 20^0 to 25^0C (68^0 to 77^0F) (See USP Controlled Room Temperature).

4. Dispensing Recommendations:
NDA - None
ANDA – None

5. Product Line:

The innovator markets 5 gram tubes with occlusive dressing, 30 gram tubes without dressing, and 1 gram anesthetic disc.

The applicant proposes to market a 30 gram tube without dressing.

6. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing Section 7 (Volume 1.2).

7. CONTAINER: [redacted]; CLOSURE: CRC/ [redacted]

8. Please note that products containing more than 5 milligrams of lidocaine in a single package require CRC packaging. This drug product is packaged in a **child resistant tube**.

9. The following is the comment forwarded to the sponsor in last deficiency letter:

We acknowledge that you included "Instructions for Application" at the end of the package insert labeling as requested in our last deficiency letter. However, as addressed in a Tele-conference between Ms. Audrey Zaweski of your firm and Chan Park of the Agency on April 15, 2003, we note that you did not include the pictorial illustrations in your proposal and modified the instructions accordingly. We are aware that the pictorial illustrations appearing in the innovator's labeling may be specific to Tegaderm® contained in the innovator's 5 gm product, and other available occlusive dressings may not be identical to this particular dressing. However, we believe that inclusion of these pictorial illustrations in your labeling may help patients to use your drug product properly. In addition, we remind you that the innovator's 30 gm product also has the same instructions including the illustrations although the Tegaderm® does not accompany the 30 gm product. Please include the pictorial illustrations and revise the instructions to be the same as the innovator's except the references specific to the 5 gm product. In addition, we ask you to increase the readability of the instructions by increasing the print size, changing the format, and/or by any other means.

Response for the sponsor: The sponsor included the pictorial illustrations and revised the instructions based on the RLD labeling. However, we note that there is a slight modification in the instructions possibly in an attempt to avoid some steps, which may be specific to Tegaderm®. We find this proposal acceptable, particularly with the same pictorial illustrations with the RLD labeling.

Date of Review: 5/5/03 **Date of Submission: 4/28/03**

Primary Reviewer: Chan Pa **Date:** 5/6/03

Team Leader: Lillie Gols **Date:** 5/6/03

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ANDA: 76-453
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Review

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

ANDA Number: 76-453 Date of Submission: March 18, 2003

Applicant's Name: Altana Inc.

Established Name: Lidocaine and Prilocaine Cream, 2.5%/2.5%

Labeling Deficiencies:

1. CONTAINER - 30 gm

   Satisfactory in final print as of March 18, 2003, submission

2. CARTON - 1 x 30 gm

   Satisfactory in final print as of March 18, 2003, submission

3. INSERT

   We acknowledge that you included "Instructions for Application" at the end of the package insert labeling as requested in our last deficiency letter. However, as addressed in a Tele-conference between Ms. Audrey Zaweski of your firm and Chan Park of the Agency on April 15, 2003, we note that you did not include the pictorial illustrations in your proposal and modified the instructions accordingly. We are aware that the pictorial illustrations appearing in the innovator's labeling may be specific to Tegaderm® contained in the innovator's 5 gm product, and other available occlusive dressings may not be identical to this particular dressing. However, we believe that inclusion of these pictorial illustrations in your labeling may help patients to use your drug product properly. In addition, we remind you that the innovator's 30 gm product also has the same instructions including the illustrations although the Tegaderm® does not accompany the 30 gm product. Please include the pictorial illustrations and revise the instructions to be the same as the innovator's except the references specific to the 5 gm product. In addition, we ask you to increase the readability of the instructions by increasing the print size, changing the format, and/or by any other means.

   Please revise your labeling as instructed above and submit in final print.

   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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 grams

Satisfactory in FPL as of 3/18/03 submission (vol. 2.1)

Carton Labeling: 1s x 30 gm

Satisfactory in FPL as of 3/18/03 submission (vol. 2.1)

Professional Package Insert Labeling:

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Elma® cream
- NDA Number: 19-941/S-015
- NDA Drug Name: Elma® cream
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: S-015/ January 27, 03
- 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
- Basis of Approval for the Carton Labeling: Side-by-side

Other Comments:

FOR THE RECORD:

1. Review based on the labeling of EMLA Cream, NDA 19-941/S-015, approved January 27, 03. The labeling supplement S-014 has been superseded by S-015. S-015 provides for a change in the container-closure system.

2. Patent/ Exclusivities

   None

3. Storage Conditions:
   NDA -Store at controlled room temperature 15^0 -30^0C (59^0 - 86^0F).
   ANDA - Store at 20^0 to 25°C (68^0 to 77°F) (See USP Controlled Room Temperature).

4. Dispensing Recommendations:
   NDA - None
   ANDA – None

5. Product Line:

   The innovator markets 5 gram tubes with occlusive dressing, 30 gram tubes without dressing, and 1 gram anesthetic disc.

   The applicant proposes to market a 30 gram tube without dressing.

6. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing Section 7 (Volume 1.2).

7. CONTAINER: [redacted] CLOSURE: CRC/ [redacted]

8. Please note that products containing more than 5 milligrams of lidocaine in a single package require CRC packaging. This drug product is packaged in the child resistant tube.

9. Refer to the comment under INSERT. The sponsor still want us to fax the labeling deficiencies although all issues were addressed in the Tele-conference.

Date of Review: 4/15/03 **Date of Submission: 3/18/03**

Primary Reviewer: Chan Park /s/ - **Date:** 4/17/03

Team Leader: Lillie Golson /s/ - **Date:** 4/17/03

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ANDA: 76-453
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Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 76-453 Date of Submission: February 4, 2003

Applicant's Name: Altana Inc.

Established Name: Lidocaine and Prilocaine Cream, 2.5%/2.5%

Labeling Deficiencies:

1. CARTON - 1 x 30 gm

   a. Revise to read "Resistant" rather than '

   b. Upon further review, we ask you to include the following text:

      NOTE TO PHARMACIST: Dispense Lidocaine and Prilocaine Cream, 2.5%/2.5% with the application instructions, which are contained in the enclosed prescribing information for this drug product.

2. INSERT

   a. CLINICAL PHARMACOLOGY (Pharmacokinetics, Metabolism) - Last sentence:

      ... glucose-6-phosphate dehydrogenase deficiencies... [add "dehydrogenase"]

   b. CLINICAL STUDIES (8th paragraph, third sentence)

      Revise the text " to read "The greatest extent of analgesia, as measured by VAS pain scores, was attained after 5 to15 minutes."

   c. WARNINGS (Methmoglobinemia) - Second paragraph:

      ... glucose-6-phosphate dehydrogenase deficiencies... [add "dehydrogenase"]

   d. HOW SUPPLIED

      Upon further review, we ask you to include the "Instructions for Application" as appearing in the innovator's insert labeling. However, please delete the reference to the tube as you are not seeking for the approval of packaging size.

Please revise your labeling as instructed above and submit in final print.

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, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 grams

Satisfactory in FPL as of 2/4/03 submission (vol. 1.1)

Carton Labeling: 1s x 30 gm

Professional Package Insert Labeling:

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Elma® cream
- NDA Number: 19-941/S-015
- NDA Drug Name: Elma® cream
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: S-015/ January 27, 03
- 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
- Basis of Approval for the Carton Labeling: Side-by-side

Other Comments:

FOR THE RECORD:

1. Review based on the labeling of EMLA Cream, NDA 19-941/S-015, approved January 27, 03. The labeling supplement S-014 has been superseded by S-015. S-015 provides for a change in the container-closure system.

2. Patent/ Exclusivities

   None

3. Storage Conditions:
   NDA -Store at controlled room temperature 15^0 -30^0C (59^0 - 86^0F).
   ANDA - Store at 20^0 to 25^0C (68^0 to 77^0F) (See USP Controlled Room Temperature).

4. Dispensing Recommendations:
   NDA - None
   ANDA – None

5. Product Line:

   The innovator markets 5 gram tubes with occlusive dressing, 30 gram tubes without dressing, and 1 gram anesthetic disc.

   The applicant proposes to market a 30 gram tube without dressing.

6. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing Section 7 (Volume 1.2).

7. CONTAINER: [redacted] CLOSURE: CRC/[redacted]

8. Please note that products containing more than 5 milligrams of lidocaine in a single package require CRC packaging. This drug product is packaged in the child resistant tube.

Date of Review: 3/6/03

Primary Reviewer: Chan Park

Team Leader: Lillie Golson

Date of Submission: 2/4/03

Date: 3/6/03

Date: 3/10/03

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ANDA: 76-453
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Review

APPEARS THIS WAY
ON ORIGINAL

DEC 23 2002

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

ANDA Number: 76-453 Date of Submission: July 1, 2002

Applicant's Name: Altana Inc.

Established Name: Lidocaine and Prilocaine Cream, 2.5%/2.5%

Labeling Deficiencies:

1. GENERAL

   The established name for your proposed product is Lidocaine and Prilocaine Cream, 2.5%/2.5%. Revise your labels and labeling accordingly.

2. CONTAINER (30 grams)

   A. Add "For External Use Only"

   B. Revise the storage statement to read "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).

   C. See GENERAL Comment.

3. CARTON (IC5091,R6/02, #42)

   See CONTAINER and GENERAL comments.

4. INSERT

   DESCRIPTION

   A. GENERAL

      i. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN names stand alone as on labels or in the title of the package insert.

      ii. Replace "[redacted] with "mcg".

      iii. Delete ' [redacted]

      iv. See comment 1.

   B. DESCRIPTION

      Add "at" between "...ratio of [redacted] and "pH 7.4, and..." in the third paragraph.

   C. CLINICAL STUDIES

      Replace "[redacted] with the established name in the first sentence of the eighth paragraph.

   D. PRECAUTIONS

      i. Add a hyphen between "para" and "aminobenzoic" in the third paragraph of the "General" subsection.

      ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

a. Revise the first sentence of the first paragraph to read "Carcinogenesis – Metabolites of both lidocaine and prilocaine have been shown..."

b. Replace "[redacted]" with the established name in the last sentence of the first paragraph.

E. HOW SUPPLIED

See CONTAINER comment B.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition?
- What is the RLD on the 356(h) form:
- NDA Number:
- NDA Drug Name:
- NDA Firm:
- Date of Approval of NDA Insert and supplement #:
- Has this been verified by the MIS system for the NDA?
- Was this approval based upon an OGD labeling guidance?
- Basis of Approval for the Container Labels:
- Basis of Approval for the Carton Labeling:

Other Comments:

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	x		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

-----Original Message-----
From: Lee, Koung U
Sent: Friday, December 06, 2002 4:40 PM
To: Farahani, Mahnaz
Cc: Golson, Lillie D
Subject: Storage Temperature Statement

Mahnaz,
Does the Altana's stability data for ANDA 76-453, lidocaine and prilocaine cream, 2.5%/2.5%, support our storage recommendation? Revise the storage statement to read "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).
Please let me know. Thanks.
Koung

FOR THE RECORD:

1. Review based on the labeling of EMLA Cream, NDA 19-941/S-012, approved April 20, 2000. Although S-012 is the last approved insert labeling, it does not include labeling changes previously approved in S-011 which contains information on the use of EMLA cream for superficial minor surgery of genital mucous

membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes. S-011 was approved on January 28, 2000. The new indication approved under S-011 was also given a 3 year exclusivity. In addition to the difference with the new indication, there are other differences in the labeling between S-011 and S-012. After some investigating, it turns out that the differences in the last two approved labeling supplements was also investigated by Ms. Kimberly Compton, Regulatory Project Manager for the Division of Anesthetic, Critical Care, and Addiction Drug Products. It turns out that because there were so many differences not only between S-011 and S-012 but also in previously submitted labeling, it was decided by the division to accept labeling, submitted on January 4, 2001, designated as FPL for S-011 and S-012, to an S-014. The designation of a new supplement was appropriate since the sponsor was essentially proposing different language from that which was approved for S-011 and S-012. S-014 was reviewed and found approvable. The sponsor of EMLA was asked to change the third sentence of the seventh paragraph in the CLINICAL TRIALS (actually "STUDIES" instead of "TRIALS") section to read "the greatest anesthesia, as measured by VAS pain scores, was attained after 5-15 minutes." Basically, this review was based on the labeling approved under S-012 and the approvable labeling under S-014.

2. Patent/ Exclusivities

Patent Data –

No	Expiration	Use Code	Use	File
4562060	December 31, 2002	None	NO LABELING IMPACT	

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
I-314	Jan 28, 2003	I-314	Topical anesthetic for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes	Application may **not** be approved until after this exclusivity expires since the firm has decided to keep this indication in their proposed labeling.

3. Storage Conditions:
NDA -Store at controlled room temperature 15^0 -30^0C (59^0 - 86^0F).
ANDA - Store at controlled room temperature 15^0 -30^0C (59^0 - 86^0F). Firm is asked to revise the storage statement to read "Store at 20^0 to 25°C (68^0 to 77°F) (See USP Controlled Room Temperature).
4. Dispensing Recommendations:
NDA - None
ANDA – None
5. Product Line:
The innovator markets 5 gram tubes with occlusive dressing, 30 gram tubes without dressing, and 1 gram anesthetic disc.
The applicant proposes to market a 30 gram tube without dressing.
6. Inactive Ingredients:The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing Section 7 (Volume 1.2).
7. CONTAINER: [redacted] CLOSURE: CRC/ [redacted]
8. Please note that products containing more than 5 milligrams of lidocaine in a single package require CRC packaging.

Date of Review: 12/05/02 **Date of Submission: 7/1/02**
Primary Reviewer: Koung Lee **Date:** 12/13/02
Team Leader: Lillie Golson **Date:** 12/16/02

cc:

ANDA: 76-453
DUP/DIVISION FILE
HFD-613/Klee/LGolson (no cc)
V:/FIRMSAM/ALTANA/LTRS&REV/76453.NA1.Labeling Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

MEDICAL OFFICER REVIEW(S)

MEDICAL OFFICER REVIEW
October 10, 2000

CD #00-236
Drug Product: Lidocaine and Prilocaine
Sponsor: [redacted]
Reference Listed Drug: EMLA ® cream and patch

And

Protocol 00-022
Drug Product: Lidocaine 2.5% and Prilocaine 2.5%
Sponsor: [redacted]
Reference Listed Drug: EMLA ® cream and patch

HFD-170 was consulted about these two inquiries on bioequivalence studies for the generic equivalent of EMLA ® cream and patch. The Division concluded that a standard bioequivalence study of the 60 mg dose could be used to determine bioequivalence of the generic drug product. In addition, they indicated that the proposed clinical endpoint study submitted by Anapharm was acceptable if OGD decided that a clinical endpoint study was necessary. Should we make that recommendation, they suggested that the sponsor should submit a protocol for review prior to undertaking the study. The Division did not address the question on the skin irritation evaluation.

Recommendation: The Sponsors should be informed that a standard bioequivalence (pharmacokinetic) study should be conducted using the 60 mg dose in order to evaluate the generic drug product's bioequivalence to the reference listed drug. Because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

/S/

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER REVIEW
September 22, 2000

CD #00-236
Drug Product: Lidocaine and Prilocaine
Sponsor: [redacted]
Reference Listed Drug: EMLA ® cream and patch

The approved indication reads as follows: EMLA (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on normal intact skin.

I. Bioequivalence study with clinical endpoints

The Sponsor has submitted a synopsis of a protocol to study the clinical bioequivalence of their product to the Reference Listed Drug. This is based on the data used to support the approval of the NDA product.

Please refer the consult to the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) so they can comment on the appropriateness of the study proposed to determine the bioequivalence of the generic and innovator drug product.

II. Skin Irritation and Sensitization Studies

EMLA comes as a cream and an anesthetic disc. Dosage and administration specifies that the cream is applied as 2.5 Gm over 20 to 25 cm^2 of skin surface and covered with an occlusive dressing that is provided. The disc applies 1 Gm of drug over a 10 cm^2 surface. Both are applied for 1 hour. In clinical studies of over 1,300 EMLA cream subjects, one or more of the following reactions was noted in 56% of patients: erythema or edema at the application site, discrete purpuric or petechial reactions at the application site (rare), and hyperpigmentaion (rare). These reactions were generally mild and transient, resolving spontaneously within 1 or 2 hours. Local effects observed in the clinical trials included paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, and rash, less than 1%. In addition, allergic and anaphylactoid reactions can occur with lodocaine and prilocaine. These are characterized by urticaris, angioedema, bronchospasm, and shock.

Please refer the consult to the Division of Dermatologic and Dental Drug Products with the following question:

Given the frequency of local reactions that are observed with the use of this product, could skin irritation be evaluated during the clinical endpoint study – a single application with 24 hours of observation, and the pharmacokinetic study (same time frame)? The

frequency of local skin reactions and the type of product may make the usual recommendation to conduct 21 day skin irritation studies and a 6 week skin sensitization study inadvisable.

/S/

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

CHEMISTRY REVIEW(S)

ANDA 76-453

Lidocaine and Prilocaine Cream, 2.5%/2.5%

Altana, Inc.

Mahnaz Farahani Ph.D.
OGD Chem Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-453

2. REVIEW #: 1

3. REVIEW DATE: November 8, 2002

4. REVIEWER: Mahnaz Farahani Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	July 1, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana, Inc.
Address:	60 Baylis Road Melville, NY 11747
Representative:	Robert J. Anderson
Telephone:	631-454-7677
Fax:	631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Lidocaine and Prilocaine

9. LEGAL BASIS FOR SUBMISSION: The RLD is Emla Cream (Lidocaine and Prilocaine 2.5% / 2.5%. The patent expires December 31, 2002. There are three patent exclusivities according to information in the Orange Book.

10. PHARMACOL. CATEGORY: Topical Anesthetic

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 2.5% / 2.5%

13. ROUTE OF ADMINISTRATION: Topical

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: Lidocaine is chemically designated as , 2-diethylamino N-2,6-dimethylphenyl. Prilocaine is chemically designated N-(2-methylphenyl)-2-propylamino.

17. RELATED/SUPPORTING DOCUMENTS: N/A

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1	II	[redacted]	[redacted]	1	I	August 2/2002	
2	II	[redacted]	[redacted]	1	A	August 3/2002	
3	III	[redacted]	[redacted]	4	A		
5	III	[redacted]	[redacted]	4	A		
[redacted]	III	[redacted]	[redacted]	4	A		
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4	A		

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		

Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-453

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

Lidocaine 2.5% and prilocaine 2.5% cream is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals. It is packaged in 30 gram tubes.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N- (2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4. Prilocaine is chemically designated as propanamide, N-(2-methylphenyl)-2-(propylamino), has an octanol:water partition ratio of 25 at pH 7.4

Each gram of cream contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), Carbomer 934P (as a thickening agent), sodium hydroxide to adjust the pH to (9.0 —, and purified water to ´ —— The drug product does not contain a preservative, however it passes the USP antimicrobial effectiveness test due to the pH.

The active ingredient lidocaine (base) is a compendial item. Prilocaine (base) and the final drug product are non-compendial.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

The firm should submit the followings:

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
HFD-645/MFarahani/11/8/02
HFD-647/Gsmith/12/12/02
HFD-617/JMin/12/18/02

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 15

Page(s) of trade secret and /or confidential commercial information

ANDA 76-453

Lidocaine and Prilocaine Cream, 2.5%/2.5%

Altana, Inc.

Mahnaz Farahani Ph.D.
OGD Chem Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-453

2. REVIEW #: 2

3. REVIEW DATE: May 9, 2003

4. REVIEWER: Mahnaz Farahani Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	July 1, 2002
Amendment	February 4, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 18, 2003
Amendment	July 8, 2003
Amendment	July 14, 2003
Amendment	July 24, 2003
Amendment	July 29, 2003
Amendment	August 8, 2003
Amendment	August 11, 2003

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

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Representative:	Robert J. Anderson
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Fax:	631-756-5114

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17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	A	May 8, 2003	
[redacted]	II	[redacted]	[redacted]	1	A	August 3, 2002	
[redacted]	III	[redacted]	[redacted]	4	A		
[redacted]	III	[redacted]	[redacted]	4	A		
[redacted]	III	[redacted]	[redacted]	4	A		
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4	A		

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6 – DMF not available
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DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Approved	5/6/03	
Bioequivalence	Acceptable	3/3/03	
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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APPEARS THIS WAY
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The Chemistry Review for ANDA 76-453

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

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The active ingredient lidocaine (base) is a compendial item. Prilocaine (base) and the final drug product are non-compendial.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation
All remaining CMC issues have been resolved and the application may be approved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
HFD-645/MFarahani/5/9/03
HFD-647/GSmith/7/30/03
HFD-617/TPalat/SHo for 7/31/03

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

ADDENDUM

ANDA # 76-453 REVIEW # 3

NAME AND ADDRESS OF APPLICANT
Altana, Inc.
60 Baylis Road
Melville, NY 11747

PROPRIETARY NAME
N/A

NONPROPRIETARY NAME
Lidocaine/Prilocaine Cream
2.5%/2.5%

AMENDMENT DATE: August 8, 2003, August 11, 2003

COMMENTS
Per the 8/8/03 telephone amendment, the firm revised the Specific Gravity and Viscosity specifications to reflect actual product performance. The original Viscosity specification was reduced from [redacted] The lower limit is consistent with the viscosity for Carbomer 934 at [redacted] should be acceptable.

CONCLUSIONS AND RECOMMENDATIONS
The firm has addressed all remaining CMC issues and should be Approved.

REVIEWER:
Glen Jon Smith
Team Leader
/S/

DATE COMPLETED:
August 14, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

BIOEQUIVALENCE REVIEW(S)

MAR - 3 2003

DIVISION OF BIOEQUIVALENCE REVIEW

Team leader, Dr. Shriniwas Nerurkar's recommendations contradicting the recommendations of the primary reviewer Dr. Surendra Shrivastava.

ANDA No.	**76-453**
Drug Product Name:	**Lidocaine and Prilocaine Cream**
Strength:	**2.5/2.5% Cream**
Applicant Name:	**Altana, Inc.**
Address:	**Melville, NY**
Submission Date(s):	**July 1, 2002**
Reviewer:	**S. G. Neurkar**
File Location:	**V\firmsam\Altana\ltrs&rev\76453n20702.doc**

I. **Executive Summary: Dr. Shrivastava found the application unacceptable not because of the failure of the bioequivalence study but because of his opinion, that the bioequivalence study with PK end points is irrelevant for this product. He recommends a bioequivalence study with clinical end points. He has reviewed the bioequivalence study and found it acceptable. He also reviewed the comparative skin reaction data and found it acceptable. In his team leader's opinion, from the bioequivalence point of view, this application should be acceptable. The following are the reasons for the acceptance.**

1. The DBE management in consultation with the medical officers of the FDA has determined that a bioequivalence study with clinical end points is not necessary for this locally acting drug product and a bioequivalence study with PK end points is acceptable (The medical consult is attached). Moreover, because of the high rate of local skin reactions, the comparability of local skin reactions for the test and reference products should be evaluated during the bioequivalence study. The DBE requested comparative evaluation of the following parameters: pallor or blanching, erythema, alteration in temperature sensation, edema and skin rash for intensity and time to resolution. The parameters should be tabulated with respect to formulation.

2. On the basis of the above-mentioned recommendations, the DBE found two ANDAs (76-290 from HiTech and 76-320 from Atrix) for this drug product acceptable. Each ANDA submitted acceptable bioequivalence study with PK end points and acceptable comparative skin reaction data. Because of this precedent and the fairness issue, the DBE can not deem Altana's ANDA unacceptable.

3. The bioequivalence study with clinical end points is not as discriminatory as the bioequivalence study with PK end points. Thus, the DBE has relied on a study that provides a robust comparison of formulations (test vs. reference).

4. Dr. Shrivastava's argument that since the drug product acts topically and not systemically, the bioequivalence study with PK end points is irrelevant can be refuted on the basis of the following data. The DBE has examples where a

bioequivalence with PK end points was allowed for a topically acting drug product simply because the feasibility of a discriminatory study. For example see Dr. Shrivastava's review on Roxane's protocols (P 02-010) for mesalamine delayed release tablet. Another example is Dr. Makary's review on Vintage's ANDA (75-339) for sulfasalazine delayed release tablet. For this locally acting drug product, not only there was a bioequivalence study with PK end points but also a bioequivalence determination based on the measurement of an inactive metabolite sulfapyridine (a valid marker).

5. The DBE requests a bioequivalence study with clinical end points when i) no other properly validated study is possible (e. g. antifungal topicals) or ii) drug warrants a bioequivalence study with clinical end points (clozapine). It is the opinion of this reviewer that Lidocaine/Prilocaine cream does not fit in those two categories.

II. Recommendation

The single dose, bioequivalence study conducted by Altana Inc. on the test product, Lidocaine/Prilocaine, 2.5%/2.5% cream lot # H628 comparing it to the reference product Astra-Zeneca's EMLA Cream (Lidocaine/Prilocaine 2.5%/2.5%), lot # 111149 has been found acceptable by the Division of Bioequivalence. The comparative skin reaction data submitted by the firm are also acceptable. The test product, Altana's Lidocaine/Prilocaine Cream, 2.5%/2.5%, is bioequivalent to the reference product Astra-Zeneca's EMLA Cream (Lidocaine/Prilocaine 2.5%/2.5%).

The firm should be informed of the recommendation.

RD INITIALED BY S. NERURKAR
FD INITIALED BY S. NERURKAR

/S/ Date 2/24/2003

Concur: /S/ Date 2/28/03

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

SGN/sgn/02-12-2003/76453n20702
CC; ANDA # 76453 (original, Duplicate), HFS 655 (Snerurkar, Shrivastava), Drug File

BIOEQUVALENCE COMMENTS

ANDA 76-453 APPLICANT : ALTANA INC.

DRUG PRODUCT: Lidocaine/Prilocaine Cream 2.5%/2.5%

The Division of Bioequivalence has completed its review of the your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comment provided in this communication are preliminary. These comments are subject to revision after the review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific and regulatory issues. Please be advised that these review s may result in need for additional bioequivalence information and /or studies, or may result in a conclusion that proposed formulation is not approvable.

Sincerely yours.

for Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CC: ANDA 76-453
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

ENDORSEMENTS: (Draft and Final with Dates)
HFD-655/Shrivastava
HFD-655/Snerurkar
HFD-617/Nnwaba
HFD-650/Conner 2/28/03

2/24/03

BIOEQUIVALENCY - DEFICIENCIES SUBMISSION DATE: July 1, 2002

1. FASTING STUDY (STF)
   Clinical
   Analytical

   Strength: 2.5%/2.5% Outcome: AC

   Winbio:

   Biostudy accepted by the Team Leader and Division Director

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-453 SPONSOR : **Altana Inc.**

DRUG AND DOSAGE FORM : **Lidocaine/Prilocaine Cream**

STRENGTH(S) : **2.5%/2.5%**

TYPES OF STUDIES : **Bioequivalence study with PK end points and Skin reaction data**

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : **Bioequivalence study is acceptable. Skin reaction data are acceptable**

DISSOLUTION : **Not applicable**

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No__	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Surendra Shrivastava BRANCH : 2

INITIAL : DOES NOT CONCUR DATE : 3/12/03

TEAM LEADER : S. G. Nerurkar, BRANCH : 2

INITIAL : /S/ DATE : 3/3/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 3/3/03

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	**76-453**
Drug Product Name:	**Lidocaine and Prilocaine Cream**
Strength:	**2.5/2.5% Cream**
Applicant Name:	**Altana, Inc.**
Address:	**Melville, NY**
Submission Date(s):	**July 1, 2002**
Reviewer:	**S. P. Shrivastava**
File Location:	**V\firmsam\Altana\ltrs&rev\76453n0702.doc**

I. Executive Summary: The firm has submitted a biostudy comparing its lidocaine/prilocaine, 2.5%/2.5% cream with AstraZeneca's Emla® cream. This product is indicated as local anesthetic in surgery, etc. The firm has measured levels of lidocaine and prilocaine in blood plasma by a validated LC/MS/MS method. The 90% CI passes the 80-125%.

However, since, this product is not intended to be absorbed into the blood stream, and the bioavailability assessed by measuring plasma levels during 36 hour period does not measure or reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.23(a)(1)] during 0-4 hour treatment period, the pharmacokinetic approach to establishing bioequivalence of this product, from this reviewer's point of view, is not appropriate. The firm is requested to conduct clinical study to establish bioequivalence of this product.

II. Submission Summary

A. Drug Product Information

Test Product	Lidocaine and Prilocaine, 2.5/2.5% Cream, Lot #H628 Manuf. Date 02/02)
Reference Product	Emla® Cream 2.5/2.5%, Lot #111149, Exp. Date 11/04
Indication	Topical anesthetic for use on dermal and genital mucous membranes

B. Contents of Submission

					How many?
Single-dose study	Yes	X	No		1
Single-dose fed study	Yes		No	X	
Steady-state study	Yes		No	X	
In vitro dissolution testing	Yes		No	X	
Waiver requests	Yes		No	X	
BCS data	Yes		No	X	
Vasocontrictor studies	Yes		No	X	
Clinical endpoints	Yes		No	X	

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No. of subjects with samples analyzed 22

Subjects	Healthy	x	Patients	☐
Sex(es) included	Male	x	Female	x

Test product Lidocaine and prilocaine cream (Altana)
Reference product Emla® Cream (AstraZenica)
Strength tested 2.5/2.5%
Dose 50 g
Summary of Statistical Analysis (Company Data)

Parameter	Point Estimate	90% Confidence Interval
$LAUC_{0-t}$	0.99	0.94-1.05
$LAUC_{0-inf}$	1.02	0.96-1.08
LC_{max}	0.98	0.90-1.06

Clinical Adverse Events

There were no serious adverse events reported. Skin reactions, e.g., skin tone change, (pallor/erythema), skin rash and local temperature sensation were rated for each subject for each treatment. Mean results are tabulated for each product:

Edema

Mean	Test 0 Hr.	Test 4 Hr.	Test 6 Hr.	Test 12 Hr.	Test 24 Hr.	Ref. 0 Hr.	Ref. 4 Hr.	Ref. 6 Hr.	Ref. 12 Hr.	Ref. 24 Hr.
Mean	0	0.04	0	0	0	0	0	0	0	0
S.D.	0	0.02	0	0	0	0	0	0	0	0

0=No edema; 1=Very slight edema, barely perceptible; 2=Slight edema, edges are well defined by definite raising; 3=Moderate edema, raised approximately 1 mm; 4=Severe edema raised more than 1 mm and/or extending beyond area of exposure.

Skin Rash

Mean	Test 0 Hr.	Test 4 Hr.	Test 6 Hr.	Test 12 Hr.	Test 24 Hr.	Ref. 0 Hr.	Ref. 4 Hr.	Ref. 6 Hr.	Ref. 12 Hr.	Ref. 24 Hr.
Mean	0	1.0	0.91	0.87	0.17	0	0.91	0.77	0.86	0.09
S.D.	0	0.0	0.29	0.34	0.39	0	0.29	0.53	0.56	0.29

0=No rash; 1=Mild rash (minor skin tone change, minimal edema, minimal papular response); 2=Moderate rash (moderate skin tone change, marked papules, moderate or severe edema, vesicles); 3=Severe rash (intense skin tone change, bullous or exudative eruptions, cracking, peeling, scabs, erosion, pustules).

Skin Tone Change (Pallor/Erythema)

Mean	Test 0 Hr.	Test 4 Hr.	Test 6 Hr.	Test 12 Hr.	Test 24 Hr.	Ref. 0 Hr.	Ref. 4 Hr.	Ref. 6 Hr.	Ref. 12 Hr.	Ref. 24 Hr.
Mean	0	0.17	0.83	0.87	0.13	0	0.09	0.77	0.86	0.09
S.D.	0	1.01	0.49	0.34	0.46	0	0.97	0.53	0.56	0.29

+3=Intense erythema (bright red, with or without petechia or papules)
+2=Moderate erythema (pink-red, uniform over application site)
+1=Mild erythema (faint-pink, uniform or spotty over application site)
0=No change in skin tone over application site compared to surrounding area
-1=Mild pallor (slight or indistinct outline of application site)

-2=Moderate pallor (discernable outline of application site)
-3=Intense pallor (clean distinct outline of application site)

Temperature Sensation

Mean	Test 0 Hr.	Test 4 Hr.	Test 6 Hr.	Test 12 Hr.	Test 24 Hr.	Ref. 0 Hr.	Ref. 4 Hr.	Ref. 6 Hr.	Ref. 12 Hr.	Ref. 24 Hr.
Mean	N/A	0.04	-0.13	0.04	0.17	N/A	-0.36	0.14	0.05	0
S.D.	N/A	0.61	0.56	0.39	0	N/A	0.73	0.35	0.21	0

-2=very cold sensation compared to non-dosed thigh
-1-cold sensation compared to non-dosed thigh
0=no difference in temperature sensation compared to non-dosed thigh
1=warm sensation compared to non-dosed thigh
2=hot sensation compared to non-dosed thigh

E. Formulation

The test product formulations are shown in Table 7 of the Appendix.
Inactive Ingredients within IIG limits Yes x No ☐
The formulation is acceptable Yes x No ☐

F. *In vitro* Dissolution

In vitro dissolution is acceptable Yes ☐ No ☐ N/A x

Comments: N/A

G. Waiver Request

Yes No x

The formulation is proportionally similar to that of the strength, which underwent acceptable *in vivo* testing Yes ☐ No ☐ N/A x

Acceptable dissolution testing, all strengths Yes ☐ No ☐ N/A x

H. Comments

1. Lidocaine/prilocaine, 2.5%/2.5% cream, is indicated as a topical (local) anesthetic for use on normal intact skin and genital mucous membranes. The systemic absorption of the drug product is a side effect (toxic) of the desired local effect. The amount of drug available on the surface of the skin depends on the diffusion constant, partition coefficient of drug between skin and vehicle, and concentration gradient. The systemic drug level, on the other hand, depends on number of factors, e.g., drug absorption, distribution, metabolism, elimination, patient's weight, etc. Therefore, pharmacokinetic approach is not appropriate for measuring bioavailability (efficacy) of topicals.

2. Additionally, blood levels represent only a small fraction of the total dose applied on the skin surface (i.e., absorption in 3 and 24 hrs. for lidocaine: 0.1 and 0.4%, and prilocaine: 0.15 and 0.85%, respectively). This is too small sample compared to what is bioavailable on the treated skin surface to provide any confidence in the data.

3. Since, this product is not intended to be absorbed into the blood stream, and the bioavailability assessed by measuring plasma levels do not measure or reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.23(a)(1)], the pharmacokinetic approach to establishing bioequivalence is not appropriate.

4. The firm is requested to conduct clinical study to establish bioequivalence of this product.

I. Recommendation

1. The bioequivalence study conducted under fasting conditions by Altana on its lidocaine and prilocaine 2.5%/2.5% cream, Lot #H628 comparing it to Emla® 2.5/2.5% cream, Lot #111149 manufactured by AstraZeneca has been found unacceptable due to Comment #1-3.

The firm should be informed of comments #1-4 and recommendation.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR DO NOT CONCUR WITH RECOMMENDATIONS.
FT INITIALED S. NERURKAR _____ Date _____

Concur: _____ Date _____
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

SPS/sps/12-30-02/76453n0702
cc: ANDA #76-453 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

See Review Addendum. 6 M Davit for Dale P Conner 2/28/03

APPENDIX

Individual Study Reviews

1. Single-dose Bioequivalence Study

a. Study Information

Study Number 10228219
Clinical Site [redacted]
Investigators: [redacted]
Financial Disclosure: Yes
Regulatory Considerations: Protocol, Consent Form and IRB Approval letter were available
Study Dates Period 1: 4/6/02, Period 2: 4/13/02
Analytical Site [redacted]
Analytical Investigator: [redacted]
Analysis Dates 4/17/02 – 4/27/02
Storage Period 4/6/02 – 4/27/02 = 21 Days

Financial Disclosure
The sponsor has certified that the investigator(s), has/have not entered into any financial arrangement with the sponsor, has/have no proprietary interest in the product(s), or was/were recipient(s) of significant payments of other sorts.

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Lidocaine and prilocaine	Emla®
Manufacturer	Altana	AstraZeneca
Batch/Lot No.	H628	111149
Manufacture Date	02/02	N/A
Expiration Date	N/A	11/04
Strength	2.5/2.5%	2.5/2.5%
Dosage Form	Cream	Cream
Batch Size	[redacted]	N/A
Production Batch Size	[redacted]	N/A
Potency	97.9/98.3%	
Content Uniformity	98.1/98.1%	Not provided
Formulation	Appendix, Table 7	
Dose Administered	50 g	50 g
Route of Administration	Applied dermally on thigh for 4 hours at which time the excess drug was removed.	
Number of Subjects	24 enrolled, 22 completed the study	
Demographics	Appendix, Table 8	

No. of Sequences 2	**Crossover** Yes x No ☐
No. of Periods 2	**Replicate Design** Yes ☐ No X
No. of Treatments 2	**Balanced** Yes ☐ No x
No. of Groups x	**Washout Period** 7 days
Randomization Scheme	AB: 1, 4, 5, 7, 9, 11, 14, 16, 17, 20, 21, 24 BA: 2, 3, 6, 8, 10, 12, 13, 15, 18, 19, 22, 23
Blood Sampling Times	Pre-dose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 15, 18, 24 and 36 hrs. post-dosing.
Blood Volume Collected/Sample	10 mL at each sampling time in EDTA
Blood Sample Processing/Storage	Plasma was separated and stored in a freezer at -20^0C.
IRB Approval	Yes
Informed Consent	Yes
Healthy Subjects Yes x No ☐	**Patients** Yes ☐ No x
Subjects Demographics	See Table 3
Length of Fasting	N/A
Length of Confinement	At least 10 hrs before and 10 hrs after dosing
Safety Monitoring	Vital signs prior to dosing in each period.

b. Study Results

i. Clinical

Dropout Information		
Subject No	01	16
Reason	Did not show up for Period 2 dosing	Withdrew from study after 5-hr blood sampling in Period 1 due to feeling faint during the 5 hour period
Period	2	1
Replacement	N	N

Adverse Events	A total of 2 adverse events, one for Treatment A and one for Treatment B (Feeling faint and Itchy leg respectively)

Protocol Deviations	None

ii. Analytical Method Validation [NOT TO BE RELEASED UNDER FOI]

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D. During Study Assay Results: Lidocaine

[redacted]

E. During Study Assay Results: Prilocaine

[redacted]

Reassays

Values above the Limit of Quantitation	17
Unknown Processing Error	7
A Peak in Zero Hour Sample	3
Low Internal Standard	1

Comments: None

Conclusion: Analytical method is complete.

iii. Comments on Pharmacokinetics/Statistical Analyses

Lidocaine

1. The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals (Fig P-1, Tables 1-3). The reported values are in good agreement with those obtained by the reviewer. The 90% confidence intervals for $LAUC_{0\text{-}t}$, $LAUC_{0\text{-}inf}$, and LC_{max} are within acceptable limits. There were statistically significant period effects on AUCs and Cmax.

2. Number of subjects with the following:
   a. measurable drug concentrations at 0 hr: none
   b. first scheduled post-dose sampling time as T_{max} : none
   c. first measurable drug concentration as C_{max} : none

3. Ke and $AUC_{0\text{-}inf}$ were determined for 18 subjects.

Prilocaine

4. The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals (Fig P-2, Tables 4-6). The reported values are in good agreement with those obtained by the reviewer. The 90% confidence intervals for $LAUC_{0\text{-}t}$, $LAUC_{0\text{-}inf}$, and LC_{max} are within acceptable limits. There were statistically significant period effects on AUCs and Cmax.

5. Number of subjects with the following:
   a. measurable drug concentrations at 0 hr: none
   b. first scheduled post-dose sampling time as T_{max} : none
   c. first measurable drug concentration as C_{max} : none

6. Ke and $AUC_{0\text{-}inf}$ were determined for 17 subjects.

7. Lidocaine/prilocaine, 2.5%/2.5% cream, is indicated as a topical (local) anesthetic for use on normal intact skin and genital mucous membranes. The systemic absorption of the drug product is a side effect (toxic) of the desired local effect. The amount of drug available on the surface of the skin depends on the diffusion constant, partition coefficient of drug between skin and vehicle, and concentration gradient. The systemic drug level, on the other hand, depends on number of factors, e.g., drug absorption, distribution, metabolism, elimination, patient's weight, etc. Therefore, pharmacokinetic approach is not appropriate for measuring bioavailability (efficacy) of topicals.

8. Additionally, blood levels represent only a small fraction of the total dose applied on the skin surface (i.e., absorption in 3 and 24 hrs. for lidocaine: 0.1 and 0.4%, and prilocaine: 0.15 and 0.85%, respectively). This is too small sample compared to what is bioavailable on the treated skin surface to provide any confidence in the data.

9. Since, this product is not intended to be absorbed into the blood stream, and the bioavailability assessed by measuring plasma levels do not measure or reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.23(a)(1)], the pharmacokinetic approach to establishing bioequivalence is not appropriate.

The firm is requested to conduct clinical study to establish bioequivalence of this product.

Conclusion: The single-dose bioequivalence study is not acceptable due to comment #7-9 above.

FIG P–1. PLASMA LIDOCAINE LEVELS (N=22)

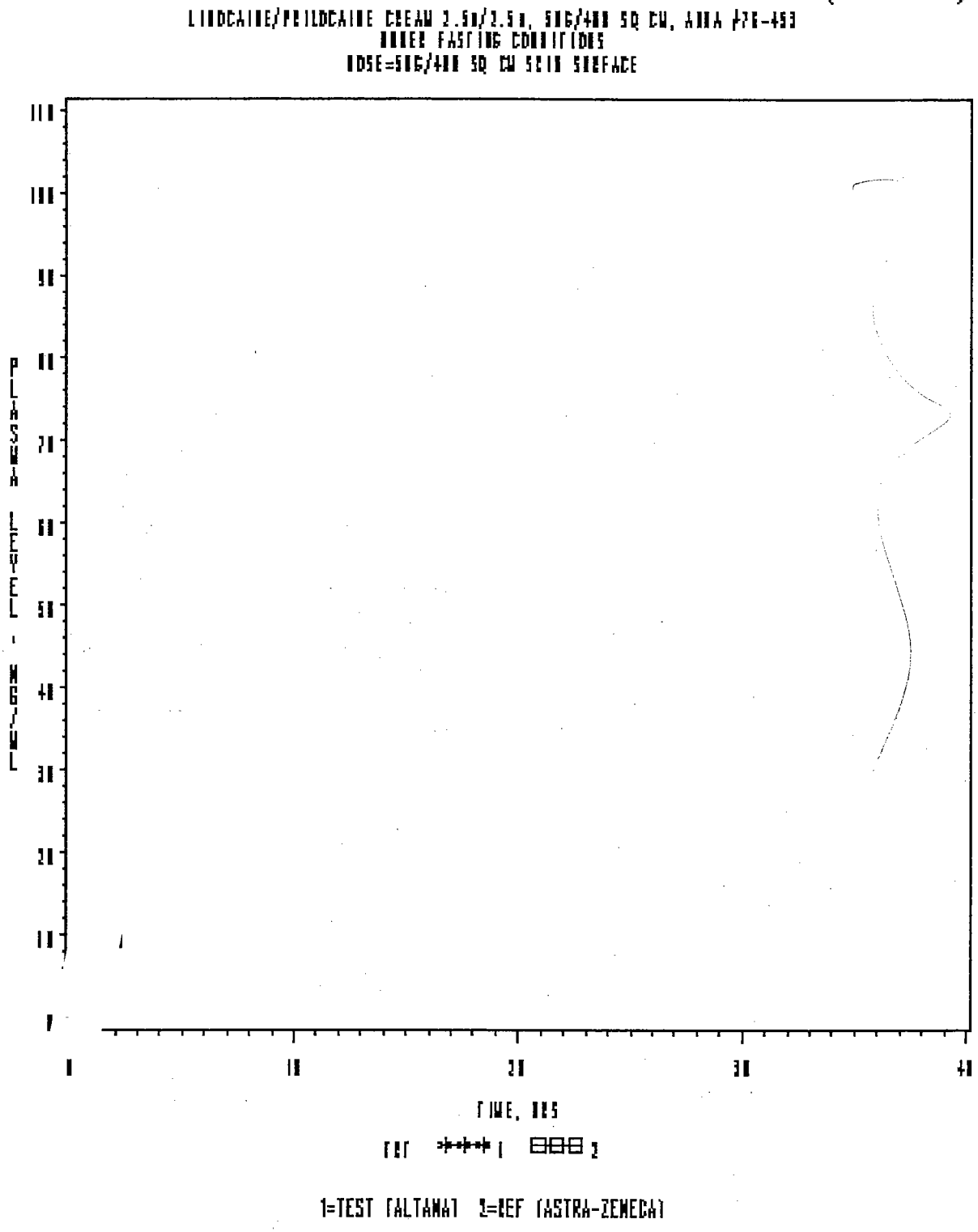


TABLE 1. MEAN PLASMA LIDOCAINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.48	0.85	0.45	0.70	1.07
2	10.38	16.54	9.48	13.87	1.10
3	38.30	41.93	36.85	43.66	1.04
4	65.49	54.50	65.44	57.70	1.00
5	98.55	56.37	101.71	66.41	0.97
6	85.53	45.51	87.73	54.87	0.97
6.5	79.96	38.51	80.71	47.70	0.99
7	82.06	40.90	83.25	45.31	0.99
7.5	81.77	40.37	78.44	37.77	1.04
8	80.21	38.14	77.87	38.05	1.03
9	68.91	32.19	66.95	31.05	1.03
10	52.87	24.59	49.79	22.29	1.06
12	38.37	18.58	37.64	19.32	1.02
15	23.47	11.20	24.63	13.90	0.95
18	14.29	8.05	14.97	7.71	0.95
24	5.53	3.09	5.40	2.73	1.02
36	1.12	0.61	1.22	0.78	0.92

MEAN1=TEST, MEAN2=REF UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 2. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	837.03	286.89	954.31	449.31	0.88
AUCT	889.40	404.01	891.16	437.75	1.00
CMAX	107.80	51.52	110.55	61.01	0.98
KE	0.15	0.04	0.16	0.04	0.95
LAUCI	787.04	0.37	860.59	0.48	0.91
LAUCT	813.91	0.43	800.52	0.48	1.02
LCMAX	96.47	0.50	95.23	0.58	1.01
THALF	4.97	1.34	4.72	1.28	1.05
TMAX	6.32	2.10	6.43	2.05	0.98

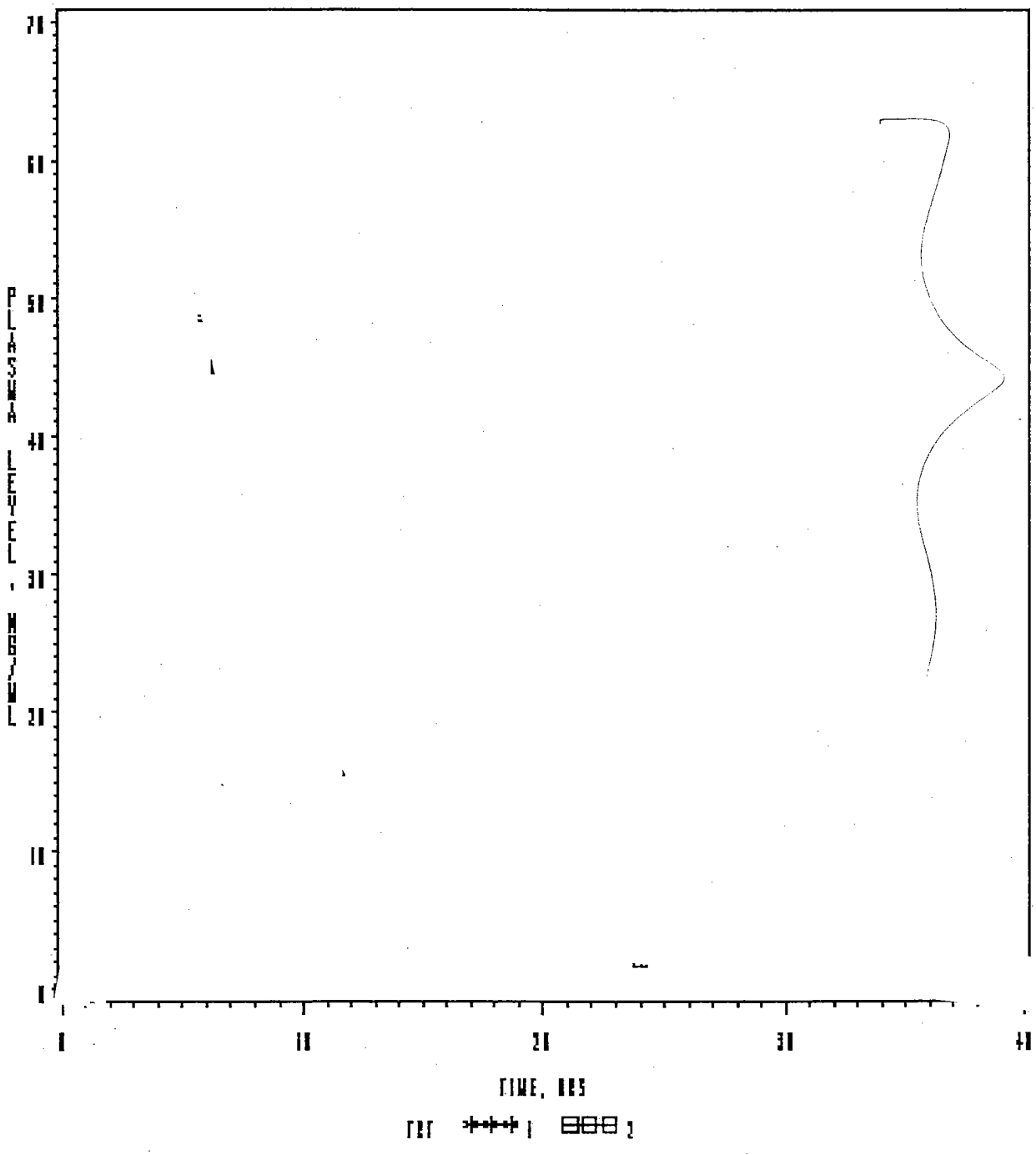
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	901.48	916.96	0.98	92.38	104.25
AUCT	891.58	900.73	0.99	94.33	103.64
CMAX	108.34	111.92	0.97	89.52	104.08
LAUCI	823.72	821.90	1.00	93.84	107.03
LAUCT	815.06	808.67	1.01	95.79	106.05
LCMAX	96.86	96.34	1.01	93.59	108.00

FIG P—2. PLASMA PRILOCAINE LEVELS (N=22)

LIDOCAINE/PRILOCAINE CREAM 2.5%/2.5%, 500MG/400 SQ CM, ANRA #78-453
UNDER FASTING CONDITIONS
DOSE=500MG/400 SQ CM SKIN SURFACE



1=TEST (ALTANA) 2=REF (ASTRA-ZENECA)

TABLE 4. MEAN PLASMA PRILOCAINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.21	0.40	0.19	0.36	1.10
2	6.30	10.20	5.99	9.38	1.05
3	24.19	26.75	23.55	28.89	1.03
4	40.57	33.40	40.93	36.82	0.99
5	59.20	34.44	62.23	41.50	0.95
6	48.56	25.27	50.63	31.78	0.96
6.5	44.88	21.41	45.05	26.83	1.00
7	44.75	21.88	45.20	24.81	0.99
7.5	43.64	20.29	42.28	19.83	1.03
8	41.98	18.01	41.06	18.69	1.02
9	35.77	14.32	35.20	13.84	1.02
10	26.29	10.01	24.92	8.90	1.06
12	15.86	5.89	16.15	7.01	0.98
15	8.62	2.74	9.20	3.74	0.94
18	5.40	2.00	6.03	2.57	0.89
24	2.28	1.23	2.21	1.13	1.03
36	0.60	0.47	0.61	0.53	0.98

MEAN1=TEST, MEAN2=REF UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 5. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	479.24	218.24	464.55	213.76	1.03
AUCT	451.80	191.76	457.98	214.59	0.99
CMAX	62.45	32.74	65.41	39.10	0.95
KE	0.14	0.05	0.15	0.06	0.96
LAUCI	442.23	0.40	429.21	0.39	1.03
LAUCT	421.29	0.37	421.58	0.40	1.00
LCMAX	54.84	0.54	55.59	0.59	0.99
THALF	5.22	1.25	5.22	1.75	1.00
TMAX	6.27	2.12	6.16	1.82	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	471.04	469.01	1.00	95.40	105.46
AUCT	451.81	462.39	0.98	92.26	103.16
CMAX	62.60	66.29	0.94	84.83	104.04
LAUCI	439.68	432.08	1.02	96.62	107.17
LAUCT	420.24	424.42	0.99	93.77	104.55
LCMAX	54.85	56.16	0.98	89.68	106.37

Table 7. Formulation

Ingredient	Test	Reference
	Percent, w/w	
Lidocaine USP	2.5	2.5
Prilocaine	2.5	2.5
Polyoxyethylene Fatty Acid Ester	[redacted]	[redacted]
Carbomer 934 NF	[redacted]	[redacted]
Purified Water, USP	[redacted]	[redacted]
Sodium Hydroxide, NF*	[redacted]	[redacted]
* Sodium hydroxide used to adjust pH 9.00		

Table 8. Subject Demographics

Particulars	Details				
Race	Caucasian=13	Hispanic=0	Black=8	Asian=1	Other=2
Sex	Males=10	Females=14			
Age, yrs.	Ave=28.4	Range=18-55	18-39 Yrs =21; > 40 Yrs =3		
Height, in.	Ave=68.25	Range=60-76			
Weight, lbs.	Ave.= 161.5	Range=126-210			

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-453 APPLICANT: Altana

DRUG PRODUCT: Lidocaine and Prilocaine, 2.5%/2.5% Cream

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Lidocaine/prilocaine, 2.5%/2.5% cream, is indicated as a topical (local) anesthetic for use on normal intact skin and genital mucous membranes. The systemic absorption of the drug product is a side effect (toxic) of the desired local effect. The amount of drug available on the surface of the skin depends on the diffusion constant, partition coefficient of drug between skin and vehicle, and concentration gradient. The systemic drug level, on the other hand, depends on number of factors, e.g., drug absorption, distribution, metabolism, elimination, patient's weight, etc. Therefore, pharmacokinetic approach is not appropriate for measuring bioavailability (efficacy) of topicals.

2. Additionally, blood levels represent only a small fraction of the total dose applied on the skin surface (i.e., absorption in 3 and 24 hrs. for lidocaine: 0.1 and 0.4%, and prilocaine: 0.15 and 0.85%, respectively). This is too small sample compared to what is bioavailable on the treated skin surface to provide any confidence in the data.

3. Since, this product is not intended to be absorbed into the blood stream, and the bioavailability assessed by measuring plasma levels do not measure or reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.23(a)(1)], the pharmacokinetic approach to establishing bioequivalence is not appropriate.

The firm is requested to conduct clinical study to establish bioequivalence of this product.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-453
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/SShrivastava
HFD-655/SNerurkar
HFD-617/NNwaba
HFD-650/DConner

2/11/03

DO NOT CONCUR WITH RECOMMENDATIONS 2/12/03

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 7/1/2002

1. **FASTING STUDY** (STF)
Clinical:
Strength: 2.5%/2.5%
Outcome: UN
Analytical:

Outcome Decisions:
UN - Unacceptable

APPEARS THIS WAY
ON ORIGINAL

BIOEQUVALENCE COMMENTS

ANDA 76-453 APPLICANT : ALTANA INC.

DRUG PRODUCT: Lidocaine/Prilocaine Cream 2.5%/2.5%

The Division of Bioequivalence has completed its review of the your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comment provided in this communication are preliminary. These comments are subject to revision after the review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific and regulatory issues. Please be advised that these review s may result in need for additional bioequivalence information and /or studies, or may result in a conclusion that proposed formulation is not approvable.

Sincerely yours.

/S/

for Dale P. Conner, Pharm. D.
Director, Division of
Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

ADMINISTRATIVE DOCUMENTS

Telephone Conference

Date: 7/31/03

ANDA: 76-453

Firm: Altana

Industry: Audrey Zaweski

FDA: Christine Bina

Topic:

I talked to Audrey Zaweski today from Altana. I told her that all patents and exclusivities have expired. I asked her to submit a new patent certification and exclusivity statement. She will fax and follow with hard copy.

Addendum 00-236

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: October 5, 2000

TO: Harvey A. Greenberg, R.Ph.
Office of Generic Drugs

FROM: Bob A. Rappaport, M.D. /S/
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

THROUGH: Cynthia G. McCormick, M.D. /S/
Director, DACCADP

RE: Consultation re: EMLA generic applications; ODE II CTSR
Document ID #'s: 2764 and 2766

We recently received two separate consults from the Office of Generic Drugs regarding the matter of establishing bioequivalence for the first generic product to reference EMLA. The first consult dated September 6, 2000 [#2764] includes a memorandum from Jenny Lee. Ms. Lee notes that the Division of Bioequivalence has received an inquiry from a firm wishing to produce a generic version of EMLA. Ms. Lee reports that this firm had submitted a protocol designed to satisfy the generic regulations and she requested our comments on whether this protocol would adequately evaluate bioequivalence, or if a study with clinical or pharmacodynamic endpoints would be more meaningful.

Under this protocol, 36 subjects entered into the study would receive 60 mg of the test or reference product in a single-dose, crossover design. After four hours, during which time the application site will be covered with an occlusive dressing, the drug is to be removed. Blood samples are to be collected pre-dose and up to 12 hours after drug removal. No clinical or pharmacodynamic endpoint measurements are planned.

The second consult dated September 25, 2000 [#2766] includes two facsimiles sent to OGD by [redacted] The first asks whether a standard bioequivalence study would be acceptable for an ANDA referencing EMLA. The second facsimile includes a clinical study synopsis and asks whether this study design would be acceptable should a clinical bioequivalence trial be required by OGD. Also included in this consult is a review by Dr. Mary Fanning that requests referral to DACCADP for comment on the proposed clinical bioequivalence study.

Under [redacted] protocol, 60 healthy volunteers entered into the study would receive an unspecified quantity of the test or reference product in a single-dose, crossover design. After one-hour, during which time the application site would be covered with an occlusive dressing, the drug is to be removed. The primary outcome measurement is to be pain on a VAS using the average of three pinpricks over the applied area and over an unanesthetized area. Efficacy evaluation is to take place at 1, 1.5, 2, and 3 hours post-application. Local reaction at the application site would also be assessed at 1, 2, 3 and 24 hours post-application. Safety monitoring would include routine examination, ECG, vital signs, hematology, and serum chemistry.

The original application for EMLA included an *in-vitro* skin penetration study, which compared 5% EMLA to 30% lidocaine cream. That study showed a 6.5 fold increase in penetrability of the EMLA compared to the lidocaine in excised human skin. A second study was required by the Agency that would fulfill the fixed-dose, combination-drug regulations. That study consisted of randomization of patients to a single-dose, double-blind, placebo-controlled, factorial-design trial, which tested eight skin sites, four each at 30 and 60 minutes. The efficacy endpoints included pain from pinprick and needle insertion measured on a VAS. Multiple placebo and active-controlled studies of the effectiveness and safety of EMLA were undertaken in normal subjects as well as pediatric and adult patients. The efficacy outcome measure for these studies was pain due to either pinprick, venipuncture or split-thickness skin grafting.

Blood samples obtained during a pharmocokinetic study documented that a full set of pharmacokinetic data could be obtained after the application of a 60-mg dose. Therefore, it would seem appropriate that a standard bioequivalence study could be the accepted criterion for approval of a generic product using EMLA as the reference listed drug.

Should OGD determine that a clinical bioequivalence study would also be required, the basic design of the proposed [redacted] study should be acceptable. However, a review of the actual protocol by our Division is recommended prior to approving the sponsor's clinical development plan, as the current protocol synopsis provides minimal information.

Cc: HFD-170:
Jenkins
McCormick
Rappaport
Blatt

#FOO-0008

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO *(Division/Office)* ODE – 2, HFD-102, Leah Ripper --forward to HFD-170, Division of Anesthetic , Critical Care & Addiction Drug Products			FROM: OGD/ Reg Support Branch HFD-615	
DATE: September 25, 2000	IND NO.	ANDA NO. Control Document 00-236	TYPE OF DOCUMENT	DATE OF DOCUMENT June 19, 2000
NAME OF DRUG Lidocaine and Prilocaine Cream and Patch		PRIORITY CONSIDERATION Medium	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 25, 2000
NAME OF FIRM [redacted]				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICPENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- *X OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END QF PHASE II MEETING ☐ CONTROLLED STUDI ES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III.BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV.DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE. DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

x☐ CLINICAL ☐ PRECLINICAL

COMMENTS

The firm submitted a control document comments for proposed studies, Dr.Fanning has completed the initial review and provided comments . Please review and provide comments or concurr with her comments.
Thank you,
Harvey

Please return completed review :

Harvey Greenberg
Office of Generic Drugs
RSB/ HFD-615

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* ☐ MAIL ☐ HAND
arvey Greenberg	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

#2766

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-453

CORRESPONDENCE

ANDA 76-453

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

APPLICANT: Altana, Inc.

TEL: 631-454-7677

ATTN: Audrey Zaweski

FAX: 631-756-5114

FROM: Ted Palat

PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 1, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

We are pleased to inform you that this application is APPROVED!

8-12-03

FILE IN ANDA 76-453 (MC)

Pharma

ALTANA

Fax

ALTANA Inc.
60 Baylis Road
Melville, NY 11747
USA
T+1 (631) 464-7677
www.altanainc.com

To Ted Palat

FDA

Fax 301-443-3839

From Audrey Zaweski, *Associate Director* Regulatory Affairs

Date July 30, 2003

Pages including cover sheet 5

Extension Phone/Fax
Ext. 3007
631-756-5114
azaweskl@altanainc.com

Subject: **ANDA 76-453**
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

If you should have any questions, please do not hesitate to get back to me.

Sincerely,
ALTANA Inc.

Audrey Zaweski

Pharma

ALTANA

July 30, 2003

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Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-640)
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA Telefax (301) 594-0183 and FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Ms. Fang:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the July 30, 2003 FDA Telephone Contact from Ms. Sarah Ho. Ms. Ho was reviewing the most recent Altana Telephone Amendment dated July 29, 2003 and has requested the following commitment.

Altana commits to work with FDA to respond to the request for Methods Validation Samples and work expeditiously to resolve any deficiencies from the Methods Validation Study.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski AR

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA:jb

Pharma

ALTANA

July 29, 2003

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-640)
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N/AM

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www.altanainc.com

VIA Telefax (301) 594-0183 and FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Ms. Fang:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the July 29, 2003 FDA Telephone Contact from Glen Jon Smith. Mr. Smith was reviewing the most recent Altana Telephone Amendment dated July 24, 2003 and has requested additional information.

Altana Inc. has prepared this Telephone Amendment in response to the July 29th Teleconference. This Amendment has been prepared in **comment**/response format.

Please revise your Specifications for the degradation products: [redacted] and others.

Altana has revised the Degradation Product Specifications as requested. Copies of the In-Process, Finished Product and Stability Specifications are included as **Attachment I.**

Please re-submit the Analytical Procedure that was included in the July 24, 2003 Telephone Amendment.

Altana has included the Analytical Procedure as **Attachment II.**

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RECEIVED
JUL 30 2003
OGD/CDER

Pharma

ALTANA

July 24, 2003

ORIG AMENDMENT

N/A

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Florence Fang
Director
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Food and Drug Administration
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7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA Telefax (301) 594-0183 and FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Ms. Fang:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the July 15, 2003 FDA Telephone Contact from Tom Palat and Glen Jon Smith. Mr. Smith was reviewing the most recent Altana Telephone Amendment and had a question.

Altana Inc. has prepared this Telephone Amendment in response to the July 15th Teleconference. This Amendment has been prepared in **comment**/response format.

1. **In reviewing Altana's most recent Telephone Amendment against the Methods Validation Report submitted in the original application, specifically page 2420, there is an The report states this . Is Altana measuring something else at Please provide data to support that Altana is in fact measuring**

   Altana has conducted an experiment to confirm the identity of the peak. A summary of the results and associated chromatographs are included as Attachment I.

   As a result of this study, Altana Inc. has revised the stability specifications and the analytical procedure for the drug product. See Attachment II.

RECEIVED
JUL 25 2003
OGD/CDER

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Zaweski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

Pharma

ALTANA

July 14, 2003

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-640)
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
7/14/03

ALTANA Inc
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VIA Telefax (301) 594-0183 and
FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Ms. Fang:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the July 8, 2003 Telephone Amendment which included updated controlled room temperature stability data.

Altana Inc. has prepared this Telephone Amendment in response to a request by Ted Palat and Glen Smith in a July 10, 2003 teleconference with Altana. This Amendment has been prepared in **comment**/response format.

1. **Please add a specification for [redacted] on the Lidocaine Raw Material Specifications. The vendor's Certificate of Analysis states NMT [redacted]**

   Altana has updated the raw material specification to include [redacted] at NMT [redacted]. Included in **Attachment I** are the revised Raw Material Specifications and Annual Retest Specifcation (12 month extension).

2. **Please revise your stability specifications for the degradation product at RRT [redacted] based on observed data.**

   Altana has revised the Stability Specifications for RRT [redacted] nd RRT [redacted] as stated below.
   [redacted]: not more than [redacted]
   [redacted] not more than [redacted]

   These limits are the same as the limits on the Finished Product Specifications. Included in **Attachment II** are revised Stability Specifications.

RECEIVED
JUL 15 2003
OGD/CDER

3. **Please revise the specification for Total Degradation Products based on observed data.**

   The specification for total degradation products encompasses the results from all peaks noted and was reduced from NMT [redacted] to NMT [redacted]. Linear regression analysis demonstrates the predicted value at 24 months to be approximately [redacted] with a correlation coefficient of [redacted] Refer to **Attachment II** for a copy of the revised specifications.

4. **Please compare your data for [redacted] to the reference product and justify your limit.**

   Altana performed a linear regression analysis to compare the Altana product to the Reference Listed Drug (RLD) product using controlled room temperature (CRT) stability data.

Altana Product	
Interval (months)	**Result (%)**
6	[redacted]
9	[redacted]
12	[redacted]

   Using the data points above, the predicted value at 24 months is [redacted] with a correlation coefficient of [redacted]

RLD Product	
Interval (months)	**Result (%)**
5	[redacted]
11	[redacted]
14	[redacted]

   For the RLD, using the data points above, the predicted value at 24 months is also [redacted] with a correlation coefficient of [redacted]

   The RLD has an expiration date of 10/04 printed on the tube and was placed on CRT stability at Altana in 03/02. Based on this comparison it appears that the limit of NMT [redacted] is appropriate for [redacted]

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski for

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

Pharma

ALTANA

July 8, 2003

ORIG AMENDMENT
N/Am

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
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FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Ms. Fang:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the July 8, 2003 FDA telephone request for Altana to provide a commitment to assist the FDA Laboratory in validating the analytical methodology.

As requested, Altana Inc. commits to assist the FDA Laboratories in validating the analytical methods associated with Lidocaine and Prilocaine Cream 2.5%/2.5%. We understand that this validation may be performed post approval.

Altana submitted a Minor Amendment on February 4, 2003 that included revised stability specifications. Also enclosed in this submission is updated controlled room temperature stability data which reflects these revisions.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Zaweski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

Pharma

ALTANA

June 18, 2003

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VIA Telefax (301) 594-0183 and FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
TELEPHONE AMENDMENT

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is made to the Minor Chemistry Amendment dated February 4, 2003 and the FDA telephone contact on June 17, 2003 citing minor clarifications needed. This correspondence is designated as a **TELEPHONE AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Does the 30 gram tube from [redacted] **utilize the** [redacted] **If yes, does it**

[redacted]

Please provide cycling study results for the Reference Listed Drug (RLD) product.

The cycling study is primarily a shipping/distribution study. Altana Inc. performs the cycling study to examine the effects of temperature variations on the proposed drug product that may

occur during shipping and distribution. Since Altana does not distribute the Reference Listed Drug (RLD), the cycling study is not performed on the RLD.

Please provide updated Controlled Room Temperature Stability Data.

Altana has provided updated controlled room temperature stability data in **Attachment II.**

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski for

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

APPEARS THIS WAY
ON ORIGINAL

Pharma

ALTANA

April 28, 2003

ALTANA Inc
60 Baylis Road
Melville, NY 11747
USA
T +1 (631) 454-7677
www.altanainc.com

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

VIA FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
MINOR LABELING AMENDMENT

Dear Mr. Rickman:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the FDA correspondence dated April 17, 2003 citing labeling deficiencies. This correspondence is designated as a **MINOR LABELING AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Labeling Deficiencies

1. **CONTAINER – 30 gram**
   Satisfactory in final print as of March 18, 2003 submission.

   Altana acknowledges that the container label is satisfactory in final print as of the March 18, 2003 submission.

2. **CARTON – 1 x 30 gram**

   Satisfactory in final print as of March 18, 2003 submission.

   Altana acknowledges that the carton labeling is satisfactory in final print as of the March 18, 2003 submission.

RECEIVED
APR 30 2003
OGD / CDER

2. **INSERT**

We acknowledge that you included "Instructions for Application" at the end of the package insert labeling as requested in our last deficiency letter. However, as addressed in a Tele-conference between Ms. Audrey Zaweski of your firm and Chan Park of the Agency on April 15, 2003, we note that you did not include the pictorial illustrations in your proposal and modified the instructions accordingly. We are aware that the pictorial illustrations appearing in the innovator's labeling may be specific to Tegaderm® contained in the innovator's 5 gm product, and other available occlusive dressings may not be identical to this particular dressing. However, we believe that inclusion of these pictorial illustrations in your labeling may help patients to use your drug product properly. In addition, we remind you that the innovator's 30 gm product also has the same instructions including the instructions although Tegaderm® does not accompany the 30 gm product. Please include the pictorial illustrations and revise the instructions to be the same as the innovators except the references specific to the 5 gm product. In addition, we ask you to increase the readability of the instructions by increasing the print size, changing the format, and/or by any other means.

Please revise your labeling as instructed above and submit in final print.

Altana has revised the labeling as instructed above and submitted 12 final printed copies, see **Attachment I**.

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/ogd/rld/labeling_review_branch.html

Altana acknowledges that prior to approval, it may be necessary to revise the labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, Altana has subscribed to the daily updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

APPEARS THIS WAY
ON ORIGINAL

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side by side comparison of your proposed labeling with your last submission with all differences annotated and explained.

To facilitate review of this submission, and in accordance with 21 CFR 314.94(a)(8)(iv), Altana has provided a side by side comparison of the proposed labeling with the last submission with all differences annotated and explained. **Attachment II** contains the side by side comparison of the container, carton and insert labeling.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Audrey Zaweski for

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

APPEARS THIS WAY
ON ORIGINAL

Pharma

ALTANA

March 18, 2003

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
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ORIG AMENDMENT
N/AF

VIA FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
LABELING AMENDMENT

Dear Mr. Rickman:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2.5%/2.5%.

Reference is also made to the FDA correspondence dated March 10, 2002 citing labeling deficiencies. This correspondence is designated as a **MINOR LABELING AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Labeling Deficiencies

1. **CARTON**

   a. Revise to read "Resistant" rather than " [redacted]

   Altana has revised the carton labeling to read "Resistant" rather than " [redacted]

   b. Upon further review, we ask you to include the following text:

   NOTE TO PHARMACIST: Dispense Lidocaine and Prilocaine Cream, 2.5%/2.5% with the application instructions, which are contained in the enclosed prescribing information for this drug product.

   Altana has revised the carton labeling to include the following text:

   NOTE TO PHARMACIST: Dispense Lidocaine and Prilocaine Cream, 2.5%/2.5% with the application instructions, which are contained in the enclosed prescribing information for this drug product.

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MAR 19 2003
OGD / CDER

2. **INSERT**

a. **CLINICAL PHARMACOLOGY (Pharmacokinetics, Metabolism) – Last sentence:**
…glucose-6-phosphate dehydrogenase deficiencies…[add "dehydrogenase"]

Altana has revised the statement to read…glucose-6-phosphate dehydrogenase deficiencies…[adding "dehydrogenase"]

b. **CLINICAL STUDIES (8th paragraph, third sentence)**
Revise the text " [redacted] **to read "The greatest extent of analgesia, as measured by VAS pain scores, was attained after 5 to 15 minutes."**

Altana has revised the text " [redacted] to read "The greatest extent of analgesia, as measured by VAS pain scores, was attained after 5 to 15 minutes."

c. **WARNINGS (Methmoglobinemia) – Second paragraph:**
…glucose-6-phosphate dehydrogenase deficiencies…[add "dehydrogenase"]

Altana has revised the statement to read…glucose-6-phosphate dehydrogenase deficiencies…[adding "dehydrogenase"]

d. **HOW SUPPLIED**
Upon further review, we ask you to include the "Instructions for Application" as appearing in the innovator's insert labeling. However, please delete the reference to the [redacted] tube as you are not seeking for the approval of [redacted] packaging size.

Altana has revised the current insert labeling to include the "Instructions for Application" section as in the innovator's insert labeling. However, we have deleted the reference to the [redacted] tube as we are not seeking approval of [redacted] packaging size.

Please revise your labeling as instructed above and submit in final print.

Altana has revised the labeling as instructed above and submitted 12 final printed copies for approval of this application. **Attachment I** contains 12 copies of final container (no changes), carton and insert labeling.

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/ogd/rld/labeling_review_branch.html

Altana acknowledges that prior to approval, it may be necessary to revise the labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, Altana has subscribed to the daily updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side by side comparison of your proposed labeling with your last submission with all differences annotated and explained.

To facilitate review of the submission, and in accordance with 21 CFR 314.94(a)(8)(iv), Altana has provided a side by side comparison of the proposed labeling with the last submission with all differences annotated and explained. **Attachment II** contains the side by side comparison of the container, carton and insert labeling.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, *Associate Director*, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for Audrey Zaweski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

Pharma

ALTANA

February 4, 2003

ORIG AMENDMENT

N/AM

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

VIA FEDERAL EXPRESS

ANDA 76-453
Lidocaine and Prilocaine Cream 2.5%/2.5%
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application dated July 1, 2002 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94 for Lidocaine and Prilocaine Cream, 2/5%/2.5%.

Reference is also made to the FDA correspondence dated December 23, 2002 that included Chemistry and Labeling deficiencies. As requested this correspondence is designated as a **MINOR AMENDMENT** and appears prominently in this cover letter.

Each item has been addressed in **comment**/response format.

Labeling

1. **GENERAL**
   The established name for your proposed product is Lidocaine and Prilocaine Cream, 2.5%/2.5%. Revise your labels and labeling accordingly.

   Altana has revised the established name for the proposed product to Lidocaine and Prilocaine Cream, 2.5%/2.5%.

2. **CONTAINER (30 grams)**
   A. Add "For External Use Only"

   Altana has added "For External Use Only"

   B. Revise the storage statement to read "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).

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FEB 0 5 2003
OGD / CDER

MW 2-10-04

Altana has revised the storage statement to read "Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature).

C. See GENERAL Comment.

See response to 1.

3. CARTON (IC5091, R6/02, #42)
See CONTAINER and GENERAL comments.

See response to CONTAINER and GENERAL comments.

4. INSERT
DESCRIPTION
A. **GENERAL**

i. Please note that USAN names are common nouns and should be treated as such in the text of the labeling (*i.e. lower case*). Upper case may be used when the USAN names stand alone as on labels or in the title of the package insert.

Altana acknowledges that USAN names are common nouns and should be treated as such in the text of the labeling (*i.e. lower case*). Upper case may be used when the USAN names stand alone as on labels or in the title of the package insert. The insert labeling has been revised accordingly.

ii. Replace ' with "mcg".

Altana has replaced " with "mcg".

iii. Delete terminal zeros.

Altana has deleted the where appropriate.

iv. See comment 1.

See response to comment 1.

B. DESCRIPTION
Add "at" between "...ratio of and "pH 7.4, and ..." in the third paragraph.

Altana has added "at" between "...ratio of and "pH 7.4, and ..." in the third paragraph.

C. CLINICAL STUDIES
Replace ' [redacted] ' with the established name in the first sentence of the eighth paragraph.

Altana has replaced " [redacted] " with the established name in the first sentence of the eighth paragraph.

D. PRECAUTIONS

i. Add a hyphen between "para" and "aminobezoic" in the third paragraph of the "General" subsection.

Altana has added a hyphen between "para" and "aminobezoic" in the third paragraph of the "General" subsection.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

a. revise the first sentence of the first paragraph to read "Carcinogenesis – Metabolites of both lidocaine and prilocaine have been shown..."

Altana has revised the first sentence of the first paragraph to read "Carcinogenesis – Metabolites of both lidocaine and prilocaine have been shown..."

b. Replace ' [redacted] with the established name in the last sentence of the first paragraph.

Altana has replaced ' [redacted] with the established name in the last sentence of the first paragraph.

E. HOW SUPPLIED
See CONTAINER comment B.

See response to CONTAINER comment B.

Please revise your labeling as instructed above and submit 12 final printed copies of label and labeling for a full approval of this application. In addition you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Altana has revised the labels and labeling as instructed above and submitted 12 final printed copies for a full approval of this application. **Attachment I** contains 12 copies of final container, carton and insert labeling.

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/ogd/rld/labeling_review_branch.html

Altana acknowledges that prior to approval, it may be necessary to revise the labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, Altana has subscribed to the daily updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side by side comparison of your proposed labeling with your last submission with all differences annotated and explained.

To facilitate review of the submission, and in accordance with 21 CFR 314.94(a)(8)(iv), Altana has provided a side by side comparison of the proposed labeling with the last submission with all differences annotated and explained. **Attachment II** contains the side by side comparison of the container, carton and insert labeling.

CHEMISTRY

1. **DMF # [redacted] has been found to be inadequate. The holder has been notified of the deficiencies.**

   DMF [redacted] has responded to the FDA deficiencies fax correspondence dated 08/03/02. The response from [redacted] dated October 17, 2002 is included in **Attachment III.**

   [redacted] has notified Altana that this is the latest deficiency letter they have received for DMF [redacted]. To date they have not received any communication that their response was insufficient.

2. [redacted]

   test does not seem appropriate.

Redacted 2

Page(s) of trade secret and /or confidential commercial information

A forced degradation study was performed during the validation for the drug product. Please refer to the Validation Report *Validation of the Assay of Lidocaine 2.5% and Prilocaine 2.5% Cream for Lidocaine, Prilocaine, Degradation Products and Related Substances*. This report was submitted in the original Abbreviated New Drug Application, Section 15 beginning on page 2399.

7. **The specifications for the known degradants are too high and are not supported by data accrued. Please revise and resubmit.**

The Finished Product and Stability Specifications for individual and total degradation were revised based on review of the data accrued. **See Attachment IV.**

8. **Please submit the pre-approval accelerated stability protocol for the drug product.**

Altana does not submit an accelerated stability protocol in the original application as the study is complete. The data submitted as part of the original submission represents the full accelerated study. Altana submits a protocol for the Post Approval Stability Study only.

If you have any questions or require additional information please contact Ms. Audrey Zaweski, Associate Director, Regulatory Affairs at (631) 454-7677 extension 3007. Fax communications can be made to (631) 756-5114.

Sincerely,

ALTANA INC.

for
Audrey Zaweski

Robert J. Anderson, Esq.
Sr. Director, Scientific Affairs

RJA/jb

TELEFAX DATED: 08/21/2002

ALTANA

Altana Inc. 60 Baylis Road, Melville, NY 11747 631-454-7677 Fax: 631-756-5114

TO: Arianne Camphire FAX NO: (301) 594-1174

FROM: Audrey Bialeski
Altana Inc.

NEW CORRESP
NC

OF PAGES (including this page): 5

ANDA 76-453
Lidocaine 2.5% and Prilocaine 2.5% Cream
Response to FDA Request for Information

Dear Ms. Camphire:

As requested please find a revised Exclusivity Statement for the above referenced application included with telefax. A hard copy of this submission will follow via Federal Express for delivery tomorrow morning, August 22, 2002.

If you have any questions or require additional information please contact me at (631) 454-7677 ext. 3007. Fax communication may be made to (631) 756-5114.

Sincerely,

ALTANA Inc.

Audrey Bialeski

Audrey Bialeski
Manager, Regulatory Affairs

AB/cc

RECEIVED
AUG 2 2 2002
OGD / CDER

ANDA 76-453

Altana Inc.
Attention: Robert J. Anderson
60 Baylis Road
Melville, NY 11747

AUG 21 2002

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated August 21, 2002 and your correspondence dated August 21, 2002.

NAME OF DRUG: Lidocaine and Prilocaine Cream, 2.5%/2.5%

DATE OF APPLICATION: July 1, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 2, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

July 1, 2002 *VIA FEDERAL EXPRESS*

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

505(j)(2)(A) OK
21-AUG-2002
/S/

Original Submission
Abbreviated New Drug Application
Lidocaine 2.5% and Prilocaine 2.5% Cream

Dear Sir or Madam:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with the provisions under 21 CFR §314.94, Altana Inc. is submitting this Abbreviated New Drug Application to market a new drug, **Lidocaine 2.5% and Prilocaine 2.5% Cream.**

The Reference Listed Drug (RLD) that is the basis for this submission is **EMLA® CREAM (lidocaine 2.5% and prilocaine 2.5%)** – Manufactured by Astrazeneca (Astra Pharmaceuticals, L.P.) NDA 19-941. The proposed drug, Lidocaine 2.5% and Prilocaine 2.5% Cream, contains the same active ingredient and is identical in strength, dosage form and route of administration to the RLD. All inactive ingredient amounts conform to the ranges as listed in the Inactive Ingredient Guide (January 1996).

The exhibit batch, Batch #H628, included in this application was fully packaged utilizing the 30 gram presentation for which approval is currently requested. The number of units filled for this packaging size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this six (6) volume submission, along with Form FDA 356h, is the required Patent Status and Exclusivity Statements; Draft Labeling; Bioequivalence Study; full Components and Composition statements; Raw Materials Controls, description of the Manufacturing Facilities, Manufacturing and Processing Instructions, In-Process Controls, Filling and Packaging procedures; Container/Closure System; controls for the Finished Dosage Form, Analytical Methods; Stability of the Finished Dosage Form; Environmental Assessment and Certification Requirements of the Generic Drug Enforcement Act of 1992.

A copy of the bioequivalency data diskette is provided in the front cover of the first volume of the Pharmacokinetics review copy. The file types include ASCII text files, Microsoft Word files and WordPerfect files.

All regulatory correspondence related to this Abbreviated New Drug Application should be addressed to the following:

Ms. Audrey Bialeski
Manager, Regulatory Affairs
Altana, Inc.
60 Baylis Road
Melville, NY 11747
Telephone: (631) 454-7677 X 3007
Facsimile: (631) 756-5114

A certified copy of the technical section and a copy of the Methods Validation package, are being sent to the New York District Office under separate cover.

We trust that this submission will meet your approval. Please advise if you require any additional information.

Sincerely,
ALTANA INC.

Virginia Carman for

Robert J. Anderson. Esq.
Senior Director, Scientific Affairs

RJA/ap

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

[ ]

NOV 13 2000

Reference Number: OGD# 00-236

Dear Dr. Masson:

This letter is in response to your correspondence dated June 14, 2000. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Lidocaine 2.5% and Prilocaine 2.5% Cream and Lidocaine 2.5% and Prilocaine 2.5% Topical Adhesive System (EMLA• Cream and EMLA• Anesthetic Disc). OGD and the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) provide the following comments:

1. A standard bioequivalence (pharmacokinetic) study should be conducted using the 60 mg dose in order to evaluate the generic drug product's bioequivalence to the reference listed drug.

2. Because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

3. A study protocol may be submitted to the Division of Bioequivalence for comments prior to the initiation of the study.

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

Redacted 1

Page(s) of trade secret and /or confidential commercial information