

8.1.3 Reviewer's Trial #3

Title: A Randomized, Placebo-Controlled, Clinical Trial of Lidoderm™ Patches for Analgesic Efficacy and Safety in Routine Venepuncture.

8.1.3.1 Objective/Rationale

The objective of this trial was to evaluate the efficacy and safety of Lidoderm™ Patch in reducing or eliminating the pain and discomfort associated with routine venepuncture.

8.1.3.2 Design

This was a one-day, single-site, randomized, double-blind, placebo-controlled trial of parallel design in patients who were scheduled for routine venepuncture from the antecubital vein. Randomization to the 2 treatment groups was via a balanced ratio of 2:1 (active:placebo patch).

8.1.3.3 Protocol

In order to be eligible to participate in the trial subjects had to be age 18 or older, non-allergic to lidocaine or amide type local anesthetic drugs, and possess intact, normal skin over the antecubital vein. After signing an informed consent, each qualified subject was assigned a patient study number and filled out a symptom check list. The skin over the proposed venepuncture site was inspected by the research assistant conducting the study who then applied a 5 cm x 5 cm blinded test patch to the skin. After 1 hour the test patch was removed and the blood sample was drawn in the usual manner. The subject then rated the venepuncture-induced pain, filled-out a post-application dermatologic symptom check list, and had the skin inspected again. If any localized skin irritation was noted on final examination the subject was called the next day for follow-up to check if the irritation had resolved. If the reaction persisted, the subject returned to the study site for further follow-up in 1 week.

8.1.3.3.1 Population

A total of 240 subjects were enrolled in the trial. (See Table 12 below.)

Table 12 - Investigator Site and Number of Patients Entered and Evaluable from the Randomized, Placebo-Controlled, Lidoderm™ Patches in Routine Venipuncture

Investigator/Site	Tot. Enrolled	Tot. ITT Analysis	Tot. Efficacy Analysis
Michael Rowbotham, MD Pain Center Research Clinic University of California 2233 Post Street, Suite 104 San Francisco, CA 94115	233	224	221

A summary of the demographic characteristics of the 233 evaluable patients enrolled in the trial is presented in Table 13. (See Table 13 below.) No statistically significant differences were noted for any of the variables on comparison of the 2 treatment groups.

Table 13 - Demographic and Subject Characteristics of Patients Entered in the Randomized, Placebo-Controlled, Lidoderm™ Patches in Routine Venipuncture

Characteristic	Active Patch	Placebo Patch	Total	P-Value
Number Entered	155	78	233	
Age: (years)				
Mean	37.58	40.29	38.49	0.098 ^a
SD	11.39	12.48	11.81	
Range	18.0-71.0	18.0-70.0	18.0-71.0	
Sex: (%)				
Male	62(40%)	36(46%)	98(42%)	0.370 ^b
Female	93(60%)	42(54%)	135(58%)	
Race:				
Caucasian	60(43%)	39(55%)	99(47%)	0.211 ^b
Black	42(30%)	15(21%)	57(27%)	
Hispanic	14(10%)	3(4%)	17(8%)	
Asian	12(9%)	9(13%)	21(10%)	
Other	11(8%)	5(7%)	16(8%)	
Not Reported	16	7	23	
Venipuncture Location				
Rt. Ante	77(50%)	44(59%)	121(53%)	0.217 ^b
Lt. Ante	77(50%)	31(41%)	108(47%)	
Not Reported	1	3	4	
Blood Drawn:				
Yes	153(99%)	76(97%)	229(98%)	0.481 ^c
No	2(1%)	2(3%)	4(2%)	
No. Of Needle Sticks:				
1	152(98%)	72(94%)	224(97%)	0.080 ^c
2	2(1%)	3(4%)	5(2%)	
3	1(1%)	2(3%)	3(1%)	
Not Reported	0	1	1	

^a p-values for treatment comparison from one-way analysis of variance.

^b p-values from likelihood ratio chi-square test.

^c p-values from Cochran-Mantel-Haenszel test for row mean scores.

8.1.3.3.2 Endpoints

The Sponsor studied only one efficacy parameter in this trial: a 4-point categorical scale evaluating the sensation of the needle insertion, where 0=no pain

from needle insertion, 1=slight pain from needle insertion, 2=moderate pain from needle insertion, and 3 =severe pain from needle insertion.

The safety parameter evaluated was the change in the symptom check list scores (post-treatment minus pre-treatment score) and a tabulation of any adverse events reported to have occurred associated with the use of the test articles.

8.1.3.3.3 Statistical considerations

The Sponsor did not perform any sample size, nor power calculations when designing this trial protocol.

8.1.3.4 Results

8.1.3.4.1 Populations enrolled/analyzed

Seven (7) out of the 240 patients enrolled in the trial were lost to follow-up when they failed to return to the clinic at the end of the 1-hour application time. Only 221 out of the remaining 233 patients were considered evaluable for efficacy since 12 patients required more than 1 needle stick, or had to have the venepuncture outside the treated skin area, thus failing to meet the inclusion criteria for the efficacy analysis. These 12 patients were included in the trial's safety analysis.

8.1.3.4.2 Efficacy endpoint outcomes

Using a score of "1" as equivalent to the pain associated with venepuncture as a reference point, the mean values were 0.9 and 1.0 respectively for the active patch group and for the placebo patch group. No significant difference was demonstrated between treatment groups in terms of pain during venepuncture. The following table, Table 14 (see next page), shows a summary of the pain rating scores.

8.1.3.4.3 Safety outcomes

The trial failed to demonstrate any significant differences in the symptom check list scores with regards to treatment group as summarized in Table 14. (See next page.)

8.1.3.5 Conclusions Regarding Efficacy Data

This trial showed that following a 1-hour application, the Lidoderm™ Patch is ineffective in preventing or reducing the pain associated with routine venipuncture but short-term use of the patch failed to produce any serious drug-related adverse events.

Table 14 - Table of Symptom Checklist Scores and Pain Rating from the Venepuncture Trial

Table P-2
Symptom Check-List Scores and Pain Rating
(Subjects with Blood Drawn from Treated Area)

VARIABLE	ACTIVE PATCH			PLACEBO PATCH			P-VALUE ^a
	MEAN	N	SD	MEAN	N	SD	
Symptom Check-List							
Pre-Treatment	0.2	153	0.5	0.2	76	0.6	
Post-Treatment	0.5	153	0.9	0.5	76	1.0	
Change ^b	0.3	153	0.9	0.3	76	1.0	0.902
Itching							
Pre-Treatment	0.0	153	0.0	0.0	76	0.1	
Post-Treatment	0.1	153	0.3	0.0	76	0.2	
Change	0.1	153	0.3	0.0	76	0.2	0.265
Burning Skin							
Pre-Treatment	0.0	153	0.0	0.0	76	0.0	
Post-Treatment	0.0	153	0.1	0.0	76	0.2	
Change	0.0	153	0.1	0.0	76	0.2	0.991
Numb							
Pre-Treatment	0.0	153	0.1	0.0	76	0.1	
Post-Treatment	0.1	153	0.4	0.1	76	0.3	
Change	0.1	153	0.4	0.1	76	0.3	0.617
Warm							
Pre-Treatment	0.1	153	0.4	0.1	76	0.4	
Post-Treatment	0.2	153	0.4	0.1	76	0.3	
Change	0.0	153	0.5	-0.0	76	0.5	0.622
Cool							
Pre-Treatment	0.0	153	0.2	0.1	76	0.3	
Post-Treatment	0.1	153	0.3	0.2	76	0.5	
Change	0.1	153	0.4	0.1	76	0.5	0.542
Pain Rating	0.9	153	0.6	1.0	76	0.7	0.132

^a P-values for treatment comparison from Wilcoxon Rank-Sum test.

^b Change computed as post- minus pre-treatment scores.

9 Overview of Efficacy

The 3 clinical trials submitted for review in this NDA demonstrate that while the Lidoderm™ Patch is ineffectual as a short-term topical analgesic agent for procedures such as venepuncture, it is effectual in producing long-term analgesia of pain and reducing painful allodynia associated with post-herpetic neuralgia. Although the strongest evidence for this product's efficacy is generated from the analysis of the data from the Phase 3, placebo-controlled, double-blind trial it is supported by the findings of the Phase 2, placebo-controlled, cross-over trial. The robustness of the data generated from these 2 trials may have suffered from the overall long duration of disease and severity of pain experienced by the patients who participated in these studies. On review of the CRFs, it was noted that many of these patients had disease refractory to treatment, and had been referred to the tertiary clinical trial centers as a last resort after having failed multiple treatment modalities for PHN (tricyclics, oral narcotics, intrathecal delivery of analgesics and anesthetics, nerve blocks, TENS therapy, etc...). Therefore the magnitude of the product's effectiveness may have improved if more patients with early or mild PHN pain were entered into the trials, or if there was another way to prevent or control the relief provided by the mechanical action of the placebo patch to the affected nerve endings. This is highly speculative on the part of this reviewer. The degree of impact on the trials' outcomes that these 2 uncontrollable effects had is best demonstrated by the fact that it was either sheer desperation for relief from the pain endured by these patients that drove them to willingly subject themselves to painful sensory mapping during the trials, or that the patches really do work because of a mechanically generated analgesia to the point where not a single patient dropped out from the Phase 2 or 3 efficacy trials due to a lack of efficacy after they had been dispensed test patches. This reviewer feels that the magnitude of analgesic relief experienced by the patients treated with the Lidoderm™ Patch is sufficient to prove beyond a doubt that the product truly has a beneficial effect in the treatment of PHN.

10 Overview of Safety

The Lidoderm™ Patch's safety profile will be discussed in the following sections. Overall, treatment of patients with the Lidoderm™ Patch in this submission was not reported to be associated with any systemic toxicity related to transdermal drug absorption of lidocaine. The incidence of treatment-induced local adverse events was very low, approximately only 0.9%, and resolved quickly once the patch was removed. This relatively benign safety profile is in contrast to the treatment limiting burning, stinging and erythema associated with the use of capsaicin, the only other medication approved for the treatment of PHN.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

Only one death was reported to have occurred during the drug development of this product. The patient was a 75 year-old female with a history of chronic renal

failure, on maintenance hemodialysis, hypertension, coronary artery disease, status-post a stroke with resultant left hemiparesis and mild memory loss, hyperlipidemia, abdominal aortic aneurysm, Hashimoto's Thyroiditis and status-post amputation of right great toe who died from cardiac arrest secondary to ventricular fibrillation during the home-use phase of the Phase 3 PHN trial. During this portion of the trial the patient used 3 patches for 12 hours a day. The patient had developed progressive congestive heart failure and pulmonary edema thought to be secondary to severe left ventricular dysfunction due to a silent myocardial infarction. Hemodialysis was ineffectual due to persistent hypotension unresponsive to intravenous pressor therapy and fluid challenges. Echocardiogram demonstrated a markedly low cardiac ejection fraction of 20% as compared to 50% noted 2 weeks earlier. The treating physicians felt that this patient had cardiogenic shock secondary to a myocardial infarction (MI). The patient never had elevated cardiac enzymes, but it was thought that the MI had occurred within the 2 weeks between echocardiograms. On review of the case report form, it is noted that the investigators could not draw blood for lidocaine levels during Sessions 1 And 2 due to poor venous access. This medical review concurs with the investigator's impression that it is highly unlikely that this patient's death is related to treatment with the study medication. One of her background medications was vicoden for the pain which she took faithfully as noted in the study coordinator's log every night. Vicoden is a narcotic analgesic which may have masked the pain from an acute MI in this patient who had multiple risk factors for having an MI. It is interesting to note that this patient had tried numerous treatment modalities (including elavil, nerve blocks x 2, capsaicin, TENS therapy, and narcotics) for her PHN pain which she noted in her pain questionnaire as being far worse than the pain due to child birth (the patient had 2 pregnancies - a good point of reference.) Her daughters who cared for her wrote a thank you note to the study site clinic that was in the case report form thanking the clinic staff for the care and the relief that their mother finally achieved with the Lidoderm™ Patch from her chronic PHN pain. (Note: This reviewer is trying to obtain from the Sponsor randomization information on this patient for completeness of the safety review.)

10.1.2 Other Significant/Potentially Significant Events

The only other potentially significant event that was reported to have happened involved a 75 year-old male patient with severe, incapacitating pain from his PHN that had failed multiple therapies. This patient was being treated with an intrathecal implanted pump delivering dilaudid and tetracaine 2% (1.25 mg) intermittently to control his pain. He had been referred to the study as a last resort and had flown in with his son. The patient had just finished the first half of Session 1, when he fell in the parking lot of the clinic on his way to lunch, fracturing his hip. It was thought by the investigator that the test medication was not responsible for the fall, since the intrathecal tetracaine caused leg weakness necessitating this patient to use a cane. He was admitted to the hospital for surgical stabilization of his hip fracture and could not complete the rest of the trial. This reviewer concurs with the investigator that it is highly unlikely that the test

patch was responsible for the patient's fall.

10.1.3 Overdose Experience

There have been no reported cases of either intentional or accidental overdose of the Lidoderm™ Patch in patients. The chances of such an event happening during the development of this product may have been decreased due to the control that the Sponsor had over the supply of available Lidoderm™ Patches.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

In Appendix I are incidence tables by study treatment for Sessions 1, 2 and 3. These tables are not listed by COSTART body system but rather listed alphabetically. The majority of these complaints can easily be attributable as adverse events to background tricyclic or narcotic medications taken by patients in the trial. (See Appendix I.)

10.2.2 Laboratory Findings, Vital Signs

The Sponsor did lidocaine blood levels to determine the amount of transdermal absorption from the Lidoderm™ Patch. The systemic levels were reported well below the threshold limit for systemic lidocaine toxicity. (*See the discussion under safety parameters in sections 8.1.14.3. See also the pharmacokinetic review for drug bioavailability.*)

10.2.3 Special Studies

To help establish the Lidoderm™ Patch's topical safety profile, the Sponsor contracted an outside testing service, _____ to do a 21-day relative cumulative irritancy study, a repeat insult patch test for skin irritation/sensitization, and a photoallergy maximization test. These 3 studies will be briefly reviewed and discussed below.

I. Twenty-One Day Relative Cumulative Irritancy Study.

This was a single-center, multiple repeat exposure test to 1.3 cm x 1.3 cm pieces of the Lidoderm™ Patch. The test material was applied to the skin of the patients' dorsal torso daily for a total of 21 days. Patients were not allowed to wet or expose the test area to direct sun light during the 21-day exposure period. Each patient was scored for irritation daily. Exposure was halted when a grade 3 or 4 response to irritation was noted. The patient was considered to have completed the trial at that point. If edema was present with the erythematous reaction, it was described in context to surrounding normal skin. The maximum potential score that a patient could achieve was calculated by multiplying the maximum potential score (4) by the number of panelists who completed the trial by the number of days of evaluation (15). All twenty-five patients

who entered this trial completed it. Demographically, the subjects were: 72%(18/25) Caucasian, 24%(6/25) Hispanic, and 4%(1/25) Asian; 92%(23/25) were female and 8%(2/25) were male, with a mean age of 37 (range of 16-55 years). No erythema or edema was observed on any of the test sites treated with Lidoderm™ Patch, giving it a relative score of 0 out of a possible maximum score of 1500.

II. Two-Hundred Human Subject Repeat Insult Patch Test and Skin Irritation/Sensitization Evaluation.

This was a single-center, 24-hour, repeat exposure test to 1.3 cm x 1.3 cm pieces of the Lidoderm™ Patch. The test material was applied to the skin of patients' dorsal torso via occlusive dressings every other day for 3 consecutive weeks until a series of 9 24-hour exposures were completed. Adverse skin reactions (i.e., erythema and edema) were evaluated and measured within 24 hours of their occurrence. If a subject experience an adverse skin reaction to the test product, they were rechallenged at a previously unexposed skin site with the test material following a 10-14 day rest period. Repeat reactions if they occurred were scored at 24 and 48 hours post-application. Two-hundred five (205) out of the 212 patients who entered the trial completed it. Demographically, the patients were 73.1% (155/212) Caucasian, 18.4% (39/212) Hispanic, and 8.5% (18/212) Asian; 70.8% (150/212) were female and 29.2% (62/212) were male, with a mean age of 34 (range 15-57 years). No significant irritancy of any kind were reported during the course of this study.

This study was either not conducted here or not reported correctly. All patients should have been challenged after a 2 week rest period.

III. Photoallergy Maximization Test on 25 Human Subjects.

This was a single-center, dual-phase, controlled, repeat exposure test of UV-A light from a standardized, filtered source to skin that had been occluded for the preceding 24 hours with 1.3 cm x 1.3 cm of the test product, Lidoderm™ Patch. During the induction phase the, the test product and the control vehicle (hydrophilic ointment) were applied occlusively to the same skin site for 6 consecutive 24-hour periods over 3 weeks. Each exposure was followed by 3 doses of filtered light to determine the Minimal Erythral Dose (MED). The MED had been predetermined for each subject prior to testing. This was followed by the challenge phase, during which the test article was occluded for 24-hours on a previously unexposed area of skin, after which it was irradiated with 4.0 joules/cm² of UV-A light. The challenge site and a non-irradiated control site were then evaluated and scored at 48 and 72 hours post-UV-A exposure. All 25 patients who entered the trial completed it. Demographically, the patients were 88%(22/25) Caucasian, 8%(2/25) Hispanic, and 4%(1/25) Asian; 68%(17/25) were female and 32%(8/25) were male, with a mean age of 34(range 21-53 years). All subjects displayed zero scores during both the induction and challenge phases. No significant photoallergenicity was observed on any of the subjects.

Reviewer's Comments: These 3 dermal safety studies were reviewed and discussed with a dermatology medical review officer from HFD-540 who stated that the studies were appropriately conducted. (See note dated 10/9/96 filed to this NDA.) Therefore

these 3 trials demonstrate that the Lidoderm™ Patch has a very low potential to cause topical irritancy or photoallergenicity.

Discontinue

10.2.4 Drug-Demographic Interactions

Although the Sponsor went to great lengths to include a widely divergent patient population in the clinical trials with the Lidoderm™ Patch for this orphan indication, the patients that were exposed to the product were overwhelmingly caucasian, predominantly female, and geriatric with a mean age of approximately 74 years. This fact along, with the small numbers tested in the pivotal Phase 3 PHN trial make it impossible to draw any conclusions about racial, gender or age-related drug interactions with this product.

10.2.5 Drug-Disease Interactions

The Sponsor conducted a multicenter, open-label drug-disease interaction study in healthy patients with open or non-healed zoster skin lesions. The results of this trial are reviewed in detail in the PK review of this submission. This study showed that following a single topical application the transdermal absorption of lidocaine in such subjects is diminished as demonstrated by a lower AUC and maximum concentration as compared to normals, with obtainable blood levels (6 ug/ml) well below the threshold for systemic lidocaine-induced toxicity. (See the pharmacokineticist's review of this submission.)

10.2.6 Drug-Drug Interaction

In light of the fact that various strengths of both topical and systemic formulations of lidocaine have been approved and are currently marketed, the Sponsor did not perform any new drug-drug interaction studies since the drug would be expected to have the same effects as have been previously reported. (See the pharmacokineticist's review of this submission.)

10.2.7 Withdrawal Phenomena/Abuse Potential

There were no cases of withdrawal phenomena or abuse associated with the use of the Lidoderm™ Patch reported by the Sponsor in any patient that participated in the controlled trials or open-label extensions with this product. The potential for possible abuse of this product is small since the Sponsor noted early on during product development that prolonged wearing of the Lidoderm™ Patch (i.e., greater than 12 hours of application time) resulted in hypesthesia and burning sensation of the underlying skin. This was confirmed by subjects who continued to use the product during the open-label continuous/compassionate use who have reported this phenomena when they have failed to remove the Lidoderm™ Patch within the recommended time guidelines. These effects are transitory and resolve spontaneously.

10.2.8 Human Reproduction Data

In light of the fact that various strengths of both topical and systemic formulations of lidocaine have been approved and are currently marketed, the Sponsor did not perform any new preclinical reproductive and fertility studies since the drug would be expected to have the same effects as have been previously reported. *(See the animal pharmacology and toxicity review of this submission.)*

11 Labeling Review

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11

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information

13 Conclusions

At the present time there is only one drug currently marketed in the U.S. approved for the indication of treatment of pain due to post-herpetic neuralgia, and that is capsaicin. Shortly after this NDA was filed, a review article on the drug treatment of PHN appeared in The New England Journal of Medicine (1996;335:32-40.) (See Appendix II.) This article stated that although capsaicin had demonstrated statistically significant efficacy in the treatment of PHN in a clinical trial, many clinicians believe it does not work as effectively due to the burning pain sensation it induces on application. The authors cited literature on the use of topical lidocaine in the treatment of PHN that was written by the principle investigators of the trials reviewed in this submission. In fact, the data cited was the data generated from these NDA trials which was the basis for the treatment recommendations made by the authors of the article to use topical lidocaine or lidocaine-prilocaine products as first-line therapy in the treatment of PHN.

After reviewing the data presented in this NDA submission this medical reviewer concurs that the Lidoderm™ Patch is an effective treatment in the relief of acute allodynia (painful hypersensitivity) and the chronic pain associated with post-herpetic neuralgia (PHN). In addition the Lidoderm™ Patch as a topical agent offers an excellent risk: benefit ratio particularly to elderly patients who are at the greatest risk for developing this debilitating condition, as well as for adverse events to drugs used commonly off-label to treat it due to its fairly benign safety profile. Although it may not be the most effective medication in the treatment of PHN, it has a role in the chronic management of this condition.

14 Recommendations

This medical reviewer recommends that the Lidoderm™ Patch (5%) be approved for the treatment of acute allodynia and the chronic pain associated with the orphan indication of post-herpetic neuralgia pending resolution of the previously identified EA issues and consensus with the Sponsor and the reviewing division re: various labeling issues.

Since the risk of developing post-herpetic neuralgia increases with age, and is rare in the pediatric age group, there is no reason to seek a Phase 4 commitment from the Sponsor to do pediatric trials.

/S/

Rosemarie Neuner, MD, MPH
Reviewing Medical Officer

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cc: orig NDA
HFD-550
HFD-340
HFD-550/MO/Neuner
HFD-550/MO Team Leader/Hyde
HFD-550/Act Div Dir/Chambers
HFD-550/Chem/Yaciw

See Medical Officer Team Leader Review of 3/22/97

J Hyde 3/22/97

*Disagree with conclusions and recommendations
in this review. See Medical Officer Team
Leader Review.*

Acting Dir 4/10/97
Acting Div Director

Table A-6.1
Incident of Events by Study Treatment for USSF and UW Sites
Sessions 1 and 2, Pre Treatment

Classification	Placebo Patch	Active Patch
Number of Subjects	52	100
Abdominal cramps	1 (2%)	4 (4%)
Bitter taste	4 (8%)	13 (12%)
Blurred vision	7 (13%)	16 (15%)
Burning skin	31 (60%)	54 (50%)
Chills	2 (4%)	12 (11%)
Confusion	2 (4%)	4 (4%)
Constipation	9 (17%)	15 (14%)
Diarrhea	1 (2%)	7 (6%)
Dizzy	0 (0%)	13 (12%)
Dry mouth	11 (21%)	43 (40%)
Flushed feeling	3 (6%)	13 (12%)
Headache	8 (15%)	16 (15%)
Itching skin	24 (46%)	49 (45%)
Jumpy legs	2 (4%)	3 (3%)
Loss appetite	4 (8%)	15 (14%)
Light-headed	5 (10%)	13 (12%)
Muscle spasms	7 (13%)	6 (6%)
Nausea	0 (0%)	3 (3%)
Palpitations	1 (2%)	1 (1%)
Poor coordination	5 (10%)	11 (10%)
Ruddened skin	4 (8%)	12 (11%)
Ringing in ears	14 (27%)	25 (23%)
Sensitive skin	42 (81%)	80 (74%)
Shortness of breath	14 (27%)	25 (23%)
Sleepiness	17 (33%)	27 (25%)
Slow urination	13 (25%)	17 (16%)
Sneezing	9 (17%)	0 (0%)
Stuffy nose	14 (27%)	31 (29%)
Tremor	6 (12%)	0 (0%)
Weakness	8 (15%)	26 (24%)

Note: The most severe pre treatment adverse event was retained for subjects experiencing more than one occurrence of an event throughout both sessions.

Percentage rate equals the number of adverse events per 100 subjects exposed to treatment.

SOURCE: KR/BIOW/STUDY-4/ABINC)_1 (Oct 9, 1996 10:26)

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APPENDIX I

MIND HEALTH CARE, INC.
CONFIDENTIAL AND PROPRIETARY

LIDOCAINE PATCH, MULTICENTER STUDY
FINAL REPORT, IND NUMBER [REDACTED]

Table A-6.2
Incident of Events by Study Treatment for UCSF and UW Sites
Sessions 1 and 2: Post-Treatment

Classification	Placebo Patch	Active Patch
Number of Subjects	52	100
Abdominal cramps	1 (2%)	4 (4%)
Bitter taste	4 (8%)	14 (13%)
Blurred vision	5 (10%)	15 (14%)
Burning skin	29 (56%)	52 (40%)
Chills	4 (8%)	14 (13%)
Confusion	1 (2%)	4 (4%)
Constipation	5 (10%)	13 (12%)
Diarrhea	2 (4%)	4 (4%)
Dizzy	4 (8%)	11 (10%)
Dry mouth	10 (19%)	36 (33%)
Flushed feeling	5 (10%)	10 (9%)
Headache	8 (15%)	17 (16%)
Itching skin	23 (44%)	40 (37%)
Jumpy legs	2 (4%)	3 (3%)
Loss appetite	2 (4%)	13 (12%)
Light headed	8 (15%)	12 (11%)
Muscle spasms	6 (12%)	3 (3%)
Nausea	4 (8%)	5 (5%)
Palpitations	2 (4%)	1 (1%)
Poor coordination	2 (4%)	9 (8%)
Reddened skin	7 (13%)	16 (15%)
Ringing in ears	13 (25%)	22 (20%)
Sensitive skin	34 (65%)	73 (68%)
Shortness of breath	9 (17%)	19 (18%)
Sleepiness	23 (44%)	37 (34%)
Slow urination	7 (13%)	14 (13%)
Sneezing	6 (12%)	7 (6%)
Stuffy nose	12 (23%)	24 (22%)
Tremor	6 (12%)	9 (8%)
Weakness	11 (21%)	23 (21%)

Note: The most severe post treatment adverse event was retained for subjects experiencing more than one occurrence of an event throughout both sessions.

Percentage rate equals the number of adverse events per 100 subjects exposed to treatment.

SOURCE: KR/HRG/UCSF/UCSD/UCSD/UCSD 2 (Oct 9, 1996 10:32)

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Table A-6.3
Incident of Events by Study Treatment for UCSF and UW Sites
Session 3: Post Treatment

Classification	Placbo Patch		Active Patch	
	Number of Subjects	%	Number of Subjects	%
Abdominal cramps	0	(0%)	3	(3%)
Bitter taste	3	(6%)	7	(7%)
Blurred vision	5	(10%)	11	(11%)
Burning skin	16	(31%)	31	(31%)
Chills	1	(2%)	5	(5%)
Contusion	0	(0%)	6	(6%)
Constipation	6	(12%)	6	(6%)
Diarrhea	1	(2%)	3	(3%)
Dizzy	1	(2%)	3	(3%)
Dry mouth	12	(24%)	24	(24%)
Flushed feeling	1	(2%)	1	(1%)
Headache	7	(14%)	4	(4%)
Itching skin	16	(31%)	23	(23%)
Jumpy legs	2	(4%)	4	(4%)
Less appetite	3	(6%)	5	(5%)
Light-headed	2	(4%)	8	(8%)
Muscle spasm	5	(10%)	1	(1%)
Nausea	0	(0%)	1	(1%)
Palpitations	0	(0%)	1	(1%)
Poor coordination	3	(6%)	2	(2%)
Reddened skin	4	(8%)	16	(16%)
Ringing in ears	11	(22%)	16	(16%)
Sensitive skin	21	(41%)	50	(50%)
Shortness of breath	3	(6%)	13	(13%)
Sleepiness	5	(10%)	19	(19%)
Slow urination	6	(12%)	6	(6%)
Sneezing	3	(6%)	6	(6%)
Stuffy nose	5	(10%)	12	(12%)
Tremor	4	(8%)	5	(5%)
Weakness	2	(4%)	10	(10%)

Note: Percentage rate equals the number of adverse events per 100 subjects exposed to treatment.

SOURCE: KG/HHCA/T0074/AETNC1_3 (Oct 9, 1996 16:35)

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