Figure 1. Mean Lidocaine Concentrations for Female Rats on Day 17 of Gestation (linear plot)

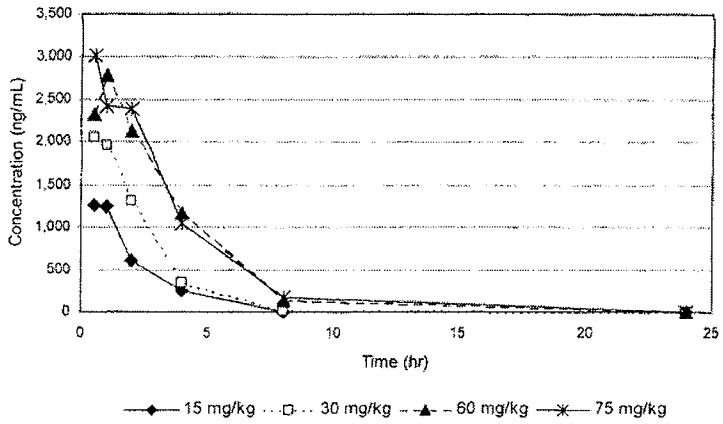

Table 1. Mean Plasma Concentrations of Lidocaine in Female Rats on Day 17 of Gestation

Time	Mean Lidocaine Concentration (ng/mL)			
	15 mg/kg	30 mg/kg	60 mg/kg	75 mg/kg
(hr)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
0.5	1,267 ± 263	2,060 ± 104	2,336 ± 281	3,019 ± 1,078
1	1,249 ± 177	1,966 ± 54	2,788 ± 504	2,430 ± 554
2	614 ± 135	1,305 ± 333	2,128 ± 271	2,397 ± 82
4	248 ± 106	349 ± 98	1,169 ± 294	1,043 ± 525
8	4.55 ± 0.80	8.35 ± 2.36	142 ± 30	176 ± 78
24	0	0.33 ± 0.57	3.62 ± 1.63	3.67 ± 3.63

n = 3

Table 2. Pharmacokinetic Parameters for Lidocaine for Female Rats on Day 17 of Gestation

Parameter	Dose			
	15 mg/kg	30 mg/kg	60 mg/kg	75 mg/kg
C_{max} (ng/mL)	1,267	2,060	2,788	3,019
T_{max} (hr)	0.5	0.5	1	0.5
AUC_{0-24} (ng*hr/mL)	3,281	5,595	11,408	11,847
r^2	0.9750	0.8786	0.9725	0.9818
k_e (hr^{-1})	0.8435	0.3521	0.2846	0.2859
$t_{1/2}$ (hr)	0.8	2.0	2.4	2.4

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): Macroscopic observations at terminal necropsy mirrored the clinical observations noted in the table above, i.e., limited to scabbing of the skin and sparse hair at the high dose lidocaine and tetracaine groups.

Two of 5 animals in the tetracaine 5 mg/kg/day dams were not pregnant; however, five of five dams in the 10 mg/kg tetracaine group were pregnant. One female in the 75 mg/kg lidocaine group was not pregnant, while one animal died while pregnant.

There were no treatment related abortions, early deliveries, complete resorptions or differences in the number of females with viable fetuses at day 20 of gestation. There were two dams in the vehicle group that had only 2 or 3 implantation sites and one dam in the 15 mg/kg lidocaine group with 2 implantation sites. These values likely contributed to some of the variability within these groups.

There were no significant differences in the mean percent post-implantation loss nonviable fetuses, resorptions (early, late or combined) between groups.

Mean gravid uterine weights in dams treated with 60 and 75 mg/kg lidocaine were increased 80% and 66% over controls (the former being statistically significant). In contrast, there were no significant changes in mean final body weights, adjusted final body weights, weight change from Day 0 or adjusted weight change from day 0 between groups. There were no treatment-related changes in fetal weight (males, females or combined) between treatment groups.

The maternal and developmental observations at the time of uterine examination and fetal observations are summarized in the table below:

Summary of Maternal and Developmental Observations at Uterine Examination (# times observed/total number of animals affected)

Group	Veh	Lidocaine				Tetracaine			
N	4	4	5	5	3	5	5	3	5
Dose (mg/kg)	**0**	**15**	**30**	**60**	**75**	**1**	**2**	**5**	**10**
Pregnancy index (%)	80	80	100	100	80	100	100	60	100
Corpora Leutea	10.5	14.8	13.6	15.2	19.3*	14.0	15.8	17.7	15.2
Implantation Sites	7.3	9.8	13.2*	13.6*	13.0	13.0*	13.6*	14.0*	13.4*
Preimplantation Loss	37.3	36.9	2.6	9.5	30.4	6.8	12.5	18.8	11.6
Viable Fetuses	6.8	9.5	12.8*	13.2*	12.7	12.2	13.2*	13.3*	13.0*
Fetal Sex Ratio	51.1	24.8	59.0	49.1	41.2	51.8	53.2	47.3	46.5
% Post implantation loss	14.6	2.1	3.0	3.1	2.8	6.7	2.9	4.8	3.1
Litter Size	6.8	9.5	12.8	13.2*	12.7*	12.2	13.2*	13.3*	13.0*
Gravid Uterine Wt (g)	42.8	57.5	73.2	77.4*	71.3	72.4	80.4*	81.7*	73.4*
No. Litters Evaluated	4	4	5	5	3	5	5	3	5
No. Fetuses Evaluated	27	38	64	66	38	61	66	40	65

Offspring (malformations, variations, etc.): The total number of litters and fetuses evaluated for external malformations and developmental variations are recorded in the table above. There were no external signs of malformations or variations observed at any dose of lidocaine or tetracaine.

Study title: Pilot Prenatal Developmental Toxicity Study in New Zealand White Rabbits (With Toxicokinetics)

Key study findings: Female New Zealand Rabbits were treated with either lidocaine or **tetracaine** on Gestation Day 7 through 20 and the maternal and fetal effects were examined with the following key findings:

1. Maternal toxicity to a varying degree was detected following both lidocaine and tetracaine at all doses of both test articles.
2. Developmental toxicity was not noted at any dose of either test article.
3. There was no effect of either lidocaine or tetracaine on the pregnancy rate, delivery time, or maternal macroscopic pathology.
4. There was no evidence for teratogenicity following either lidocaine or tetracaine at doses up to 60 mg/kg and 10 mg/kg, respectively.
5. Based upon these findings, dose levels of 1, 5 and 15 mg/kg lidocaine and 1 and 5 mg/kg/day of tetracaine were chosen for the definitive Segment II study in rabbits.

Study no.: 925-013
Volume #, and page #: Volume 4, Page 1
Conducting laboratory and location: [redacted]

Date of study initiation: January 8, 2003
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Lidocaine base, Lot 811D0013, [redacted]
Tetracaine base, Batch 721724 [redacted]

Methods

Doses: Doses of lidocaine of 30, 60, 90 and 120 mg/kg/day were initially attempted, however, the doses were reduced to 15 and 75 mg/kg, respectively due to mortality. Tetracaine doses were 1, 2, 5 or 10 mg/kg.

Species/strain: White New Zealand Rabbits, female [Hra: (NZW) SPF]

Number/sex/group: 6 per group

Route, formulation, volume, and infusion rate: Subcutaneous, phosphate buffer, volume of 1 ml/kg.

Satellite groups used for toxicokinetics: None

Study design: Nine groups of six time-mated female rabbits were administered test article on gestation days 7 to 20 via a subcutaneous injection to the scapular or lumbar regions of the back (see table below).

Group	Test Article	Dose (mg/kg/day)	Number of Animals	Mortality
1	Control	0	6	0
2	Lidocaine	30	6	0
3	Lidocaine	60	6	3
4	Lidocaine	90 – intended dose, but due to mortality lowered to 15	1 at 90 mg/kg 5 at 15 mg/kg	1 at 90 1 at 15
5	Lidocaine	120 – intended dose, but due to mortality lowered to 75	2 at 120 mg/kg 4 at 75 mg/kg	2 at 120 4 at 75
6	Tetracaine	1	6	0
7	Tetracaine	2	6	0
8	Tetracaine	5	6	0
9	Tetracaine	10	6	0

Parameters and endpoints evaluated:

Mortality and Cage Side Observations: Animals were observed twice daily for mortality and clinical signs, a detailed clinical examination was given daily from Days 7 through 29 of gestation.

Body Weight and Body Weight Changes: Body weights were recorded on Days 0, 7, 10, 13, 16, 18, 21, 25 and 29 of gestation. Individual body weight changes were calculated for the following intervals: 0-7, 7-10, 10-13, 13-16, 16-18, 18-21, 21-25, 25-29, 7-21, 21-25, 25-29, 21-29 and 0-29. Adjusted body weight (Day 29 body weight – gravid uterine weight) and adjusted body weight change (Days 0-29 of gestation) were also calculated.

Food Consumption: Food consumption was recorded daily and reported on the corresponding body weight intervals.

Toxicokinetics: Blood samples were collected on Day 20 of gestation prior to exposure and at 0.5, 1, 2 and 4 hours after treatment. Plasma samples were collected at each of the scheduled times from three animals in each dose group, except a pre-dose sample from a fourth animal. There were no animals surviving in Group 5 (75 or 120 mg/kg/day) on Day 20 of gestation and therefore no toxicokinetic data either. Blood samples were collected into vacutainers with potassium EDTA as anticoagulant and neostigmine, an esterase inhibitor (to prevent the hydrolysis of tetracaine). Levels of lidocaine and tetracaine were determined via liquid chromatography, double mass spectrometry method (LC/MS/MS). Limits of detection were 10 ng/ml and 0.9 ng/ml for lidocaine and tetracaine, respectively.

Postmortem Study Evaluations:

Maternal Necropsy: Complete necropsy was performed on all does. Gross lesions were saved and the carcass was discarded.

Ovarian and Uterine Examinations: On Day 29, each female was euthanized by sodium pentobarbital injection and exsanguination and immediately subjected to cesarean section. The skin was reflected from the ventral midline incision to examine mammary tissue and locate any subcutaneous masses. The abdominal cavity was then opened and the uterus exposed. Location of viable and non-viable fetuses, early and late resorptions, position of the cervix and total implantations were recorded. The number of corpora lutea on each ovary was recorded. The fetuses were removed and the placenta was grossly examined.

Fetal Examinations: Fetuses were individually weighed and examined for external malformations and variations. Fetuses with external malformations and or

developmental variations were preserved for possible further examination. All other fetuses were euthanized and discarded.

Results

Mortality (dams): The summary of mortalities following lidocaine treatment is presented in the table below:

Incidence of Deaths of Rabbits following Lidocaine Treatment							
Dose	0	15	30	60	75	90	120
Deaths	0/6	1/5	0/6	4/6	4/4	1/1	2/2

All rabbits treated with tetracaine survived to their scheduled termination.

Clinical signs (dams): A dose of 120 mg/kg day resulted in rapid breathing and marked decreases in activity of the dams to the point of prostration with clonic convulsions in two animals. The animals dosed at 60, 75 and 90 mg/kg exhibited these same signs. Following a dose of 30 mg/kg lidocaine there was decreased activity noted in four animals on a single day with rapid breathing in 3 of 4 animals and 2 animals on most dosing days. One animal treated with 15 mg/kg lidocaine demonstrated decreased activity, prostration, clonic convulsions and rapid breathing.

Body weight (dams): There were test article-related changes in body weight and body weight change at all doses of lidocaine and tetracaine. Body weight gains in the 15, 30 and 60 mg/kg lidocaine group over Days 7 to 21 of gestation were 155, 138 and 43 grams, respectively. This is compared to 270 grams weight in the control animals. Body weight gains in the 1, 2, 5 and 10 mg/kg tetracaine over Days 7 through 21 of gestation were 207, 215, 205 and -108 grams respectively compared to 270 grams weight in the controls.

Food consumption (dams): Maternal food consumption during gestation was decreased compared to controls at all dose levels of lidocaine during days 7 to 21 of gestation. Food consumption was decreased significantly at the 10 mg/kg/day tetracaine. Food consumption during the pretreatment and posttreatment periods was considered similar for all groups.

Toxicokinetics:

Figure 1. Mean Lidocaine Concentrations for Female Rabbits on Day 20 of Gestation (linear plot)

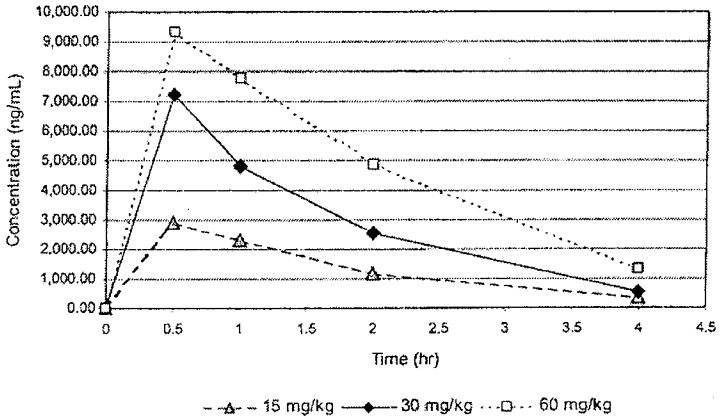

Table 1. Mean Plasma Concentrations of Lidocaine in Female Rats on Day 20 of Gestation

	Lidocaine Concentration (ng/mL)		
	15 mg/kg	30 mg/kg	60 mg/kg
Time (hr)	Mean ± SD	Mean ± SD	Mean ± SD
0	3.33 ± 6.67*	0	7.35 ± 12.72
0.5	2,928 ± 348	7,209 ± 1,922	9,327 ± 5,686
1	2,306 ± 82	4,821 ± 736	7,752 ± 2,908
2	1,164 ± 131	2,550 ± 338	4,843 ± 1,954
4	378 ± 167	556 ± 217	1,332 ± 458

n = 3, except as noted

* n = 4

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Figure 3. Mean Tetracaine Concentrations for Female Rabbits on Day 20 of Gestation (linear plot)

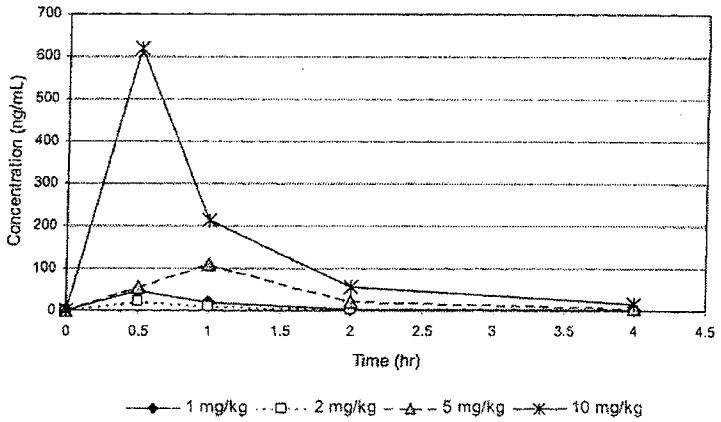

Table 2. Mean Plasma Concentrations of Tetracaine in Female Rabbits on Day 20 of Gestation

	Tetracaine Concentration (ng/mL)			
Time (hr)	1 mg/kg Mean ± SD	2 mg/kg Mean ± SD	5 mg/kg Mean ± SD	10 mg/kg Mean ± SD
0	0	0	0	0
0.5	45.68 ± 35.91	22.78 ± 20.61	56.95 ± 29.70	618.30 ± 151.48
1	19.86 ± 22.74	9.68 ± 8.56	110.81 ± 108.50	212.86 ± 110.03
2	3.40 ± 0.95	3.91 ± 3.40	22.54 ± 14.45	57.07 ± 27.83
4	1.94 ± 2.18	0.70 ± 0.61	7.67 ± 2.01	16.11 ± 11.29

n = 3 in all cases

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ON ORIGINAL

Table 3. Mean Pharmacokinetic Parameters for Lidocaine for Female Rabbits on Day 20 of Gestation

Lidocaine Parameter	15 mg/kg Dose Mean ± SD	30 mg/kg Dose Mean ± SD	60 mg/kg Dose Mean ± SD
C_{max} (ng/mL)	2,928 ± 348	7,209 ± 1,922	10,703 ± 4,624
T_{max} (hr)	0.5 ± 0.0	0.5 ± 0.0	0.7 ± 0.3
AUC_{0-24} (ng*hr/mL)	8,001 ± 1,007	16,477 ± 1,341	28,954 ± 9,675
k_e (hr^{-1})	0.5322 ± 0.2893	0.7454 ± 0.2015	0.5384 ± 0.3029
$t_{1/2}$ (hr)	1.8 ± 1.3	1.0 ± 0.3	1.7 ± 1.2

n = 3 in all cases

Table 4. Mean Pharmacokinetic Parameters for Tetracaine for Female Rabbits on Day 20 of Gestation

Parameter	1 mg/kg Dose Mean ± SD	2 mg/kg Dose Mean ± SD	5 mg/kg Dose Mean ± SD	10 mg/kg Dose Mean ± SD
C_{max} (ng/mL)	45.7 ± 35.9	22.8 ± 20.6	123.2 ± 99.3	618.3 ± 151.5
T_{max} (hr)	0.5 ± 0.0	0.5 ± 0.0	0.7 ± 0.3	0.5 ± 0.0
AUC_{0-24} (ng*hr/mL)	59.2 ± 46.0	30.5 ± 26.5	209.0 ± 56.3	683.5 ± 216.2
k_e (hr^{-1})	0.6452 *	0.8697 *	0.6488 *	0.8625 ± 0.0887
$t_{1/2}$ (hr)	1.1 *	0.8 *	1.2 *	0.8 ± 0.1

n = 3, except as noted. SD not calculated for n < 3.

* n = 2

Terminal and necroscopic evaluations:C-section data (implantation sites, pre- and post-implantation loss, etc.):

Maternal toxicity: The number of corpora lutea, implantation sites, preimplantation loss, viable fetuses, litter size, and resorptions were similar between the control group and the groups treated with lidocaine or tetracaine. There were no viable fetuses at 75 mg/kg/day lidocaine. An **increase** in post-implantation loss was seen at dose levels of 30 and 60 mg/kg/day lidocaine and 1 mg/kg/day tetracaine. Gravid uterine weights, adjusted Day 29 gestation body weights, and adjusted body weight changes from Day 0 were comparable to controls except for the 60 mg/kg/day for the treated lidocaine and tetracaine groups were

Summary of Maternal and Developmental Observations at Uterine Examination (# times observed/total number of animals affected)									
Group	**Veh**	**Lidocaine**				**Tetracaine**			
N	**6**	**6**	**6**	**6**	**6**	**5**	**5**	**3**	**5**
Dose (mg/kg)	**0**	**15**	**30**	**60**	**75**	**1**	**2**	**5**	**10**
Pregnancy index (%)	100	100	100	100	100	100	100	100	100
No. Died Pregnant	0	2	0	3	6	0	0	0	0
No. Abortions	0	0	0	1	0	0	0	0	1
% Post implantation loss	3.60	2.78	14.58	15.66	NA	16.01	7.20	7.08	0
Litter Size	9.3	7.8	7.0	9.0	NA	7.3	8.8	8.7	8.4
No. Litters Evaluated	6	4	6	2	NA	6	6	6	5
No. Fetuses Evaluated	56	31	42	17	NA	44	53	52	42
Mean Fetal Body Wt	41.95	44.83	39.73	36.02	NA	42.73	40.93	43.15	45.56

Total Malformations									
No. Litters (%)	0	0	0	0	NA	0	0	0	0
No. Fetuses (%)	0	0	0	0	NA	0	0	0	0
Total Variations									
No. Litters (%)	0	0	1	0	NA	0	0	0	0
No. Fetuses (%)	0	0	1	0	NA	0	0	0	0

NA = not applicable or not available (all animals died prior to scheduled euthanasia.

Offspring (malformations, variations, etc.):

Fetal body weights: Fetal body weights for the lidocaine and tetracaine groups did not differ statistically from controls. Mean fetal weights at 60 mg/kg/day of lidocaine was lower than controls and thought to be treatment related. Following dosing of 15 mg/kg/day of lidocaine and 10 mg/kg/day of tetracaine, fetal body weight was slightly higher than controls.

External examinations: The only external malformation noted in this study was an abnormal flexure in the forelimb and hind limb of a single fetus from 30 mg/kg/day lidocaine group. This abnormality was not considered test-article related.

Study title: Study for Effects on Embryo-Fetal Development in Rats

Key study findings: The effect of subcutaneous **lidocaine** (5, 15 and 60 mg/kg/day), **tetracaine** (5 and 10 mg/kg/day) and the **eutectic combination** of the two (10 mg/kg/day each) on the embryo-fetal development of the rat were examined with the following key findings:

1. Maternal toxicity was noted at the high doses of lidocaine, tetracaine and the combination, indicating that the study is a valid assessment of the teratogenic potential of these drugs.
2. There was no evidence of teratogenicity in any treatment under the conditions of this assay.
3. The NOAEL for maternal toxicity was 5 mg/kg/day of tetracaine and 15 mg/kg/day of lidocaine. These doses correspond to 30 and 90 mg/m^2, on a body surface area basis.
4. The NOAEL for developmental effects was 10 mg/kg/day tetracaine, 60 mg/kg/day lidocaine and 10 mg/kg/day each in a eutectic mixture. These doses correspond to 60, 360 and 60/60 mg/m^2, respectively, on a body surface area basis.

Study no.: 925-015
Volume #, and page #: Volume 5, Page 1
Conducting laboratory and location: [redacted]

Date of study initiation: February 26, 2003
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Tetracaine base, Batch # 721724, [redacted]
Lidocaine base, Lot # 811D0013

Methods

Doses: Lidocaine 5, 10 and 60 mg/kg, s.c.
Tetracaine 5 and 10 mg/kg, s.c.
Lidocaine/Tetracaine 10/10 mg/kg, s.c.

Species/strain: Sprague-Dawley rats [— CD (SD) IGS BR]

Number/sex/group: 25 as outlined in the table below:

Group Assignment		
Group Number	Dose Level (mg/kg/day)	Number of Time-mated Female Rats
1	0 (Vehicle Control)	25
2	5 (Lidocaine)	25
3	10 (Lidocaine)	25
4	60 (Lidocaine)	25
5	5 (Tetracaine)	25
6	10 (Tetracaine)	25
7	10/10 (Lidocaine/Tetracaine)	25

Route, formulation, volume, and infusion rate: Subcutaneous, vehicle was phosphate buffered saline, pH = 6.0 to 6.2, volume of 1 ml/kg. The dosing formulations were determined to be stable for 14 days when refrigerated via preliminary studies.

Satellite groups used for toxicokinetics: Not completed.

Study design: Test article and vehicle control administration began on Day 6 of gestation and continued through to include Day 17 of gestation. Individual doses were based on the most recent body weight. Test article/vehicle was administered subcutaneously in the scapular and lumbar regions of the lower back via a 26-gauge hypodermic needle. Dosing was alternated from left to right.

Parameters and endpoints evaluated:

Mortality and Clinical Signs: Animals were observed twice daily for morbidity, mortality, signs of injury and availability of food and water. Detailed clinical examinations were conducted daily from Days 6 through 20 of gestation.

Body Weights: Body weights were recorded on Days 0, 6, 9, 12, 15, 18 and 20 of gestation. Body weight changes were calculated for the following gestation day intervals: 0-6, 6-9, 9-12, 12-15, 15-18, 18-20, 6-20 and 0-20. Adjusted body weight (Day 20 gestation body weight minus gravid uterine weight) and adjusted body weight change (Days 0-20 of gestation) were also calculated.

Food Consumption: Food consumption was recorded on the corresponding body weight days and calculated for the same intervals as body weight change.

Post Mortem Evaluations: On Day 20, Dams were sacrificed by carbon dioxide inhalation and immediately subjected to cesarean section. Maternal necropsy, ovarian and uterine examinations were completed. The following were recorded: gravid uterine weight, location of viable and nonviable fetuses, early and late resorptions, position of cervix, total number of implantations, number or corpora lutea on each ovary.

Teratogenic Examinations: Fetuses were individually weighed, sexed, tagged and examined for external malformations and variations. Fetuses were euthanized via intraperitoneal injection of sodium barbital. Approximately half were placed in Bouin's

solution, the remaining in alcohol. Skeletal malformations and developmental variations were noted and classified as such under the supervision of a developmental toxicologist.

Statistical analysis: Statistical analysis was conducted according to the following table:

Statistical Analysis Methods	
Endpoint	**Analysis**
Parental In-life Data	
Gestation Body Weights	Group Pair-wise Comparisons
Gestation Body Weight Changes	Group Pair-wise Comparisons
Gestation Food Consumption	Group Pair-wise Comparisons
Adjusted Body Weights	Group Pair-wise Comparisons
Adjusted Body Weight Changes (Days 0-20)	Group Pair-wise Comparisons
Fertility Indices	
Pregnancy Index	Fisher's Exact Test
Uterine and Ovarian Exam	
Gravid Uterine Weights	Group Pair-wise Comparisons
Corpora Lutea/dam	Group Pair-wise Comparisons
Total Implantations/dam	Group Pair-wise Comparisons
Fetal Sex Ratio (% males/litter)	Arcsin-Square-Root Transformation
Litter Size/dam	Group Pair-wise Comparisons
Viable Fetuses/dam	Group Pair-wise Comparisons
Nonviable Fetuses /dam	Descriptive Statistics
Total Number Resorptions/dam	Group Pair-wise Comparisons
Number Early Resorptions/dam	Group Pair-wise Comparisons
Number Late Resorptions/dam	Group Pair-wise Comparisons
% Preimplantation Loss (mean/dam)	Arcsin-Square-Root Transformation
% Postimplantation Loss (mean/dam)	Arcsin-Square-Root Transformation
Mean Fetal Body Weights	Covariate Analysis
Malformations by finding and exam type (external, visceral, and skeletal) – litter incidence[a]	Fisher's Exact Test
Variations by finding and exam type (external, visceral, and skeletal) – litter incidence[a]	Fisher's Exact Test
Total Malformations (external, visceral, and skeletal combined) – litter incidence[a]	Fisher's Exact Test

[a]Fetal and litter incidences are reported, but only the litter incidences were statistically analyzed.

Results

Mortality (dams): Five pregnant rats treated with 10 mg/kg tetracaine were found dead on Days 6, 8, 10, 10 and 12 of gestation. These deaths were considered to be test article related.

Clinical signs (dams): Lidocaine treatment-related clinical findings were limited to prostration in one treated dam at the high dose on one occasion. In addition, dams in the high dose lidocaine group were frequently described as having hair loss or sparse hair and scabbed areas of the skin on the dorsal surface. Behavioral observations in the tetracaine treatment group included decreased activity and convulsions following 10 mg/kg doses.

Summary of Clinical Observations in the Dams (# times observed/total number of animals affected)				
Group	**Vehicle**	**Lidocaine**	**Tetracaine**	**Lido/Tet**

N	25	25	25	25	25	24	25
Dose (mg/kg)	**0**	**5**	**15**	**60**	**5**	**10**	**10/10**
Behavior							
Activity Decreased	0/0	0/0	0/0	0/0	0/0	158/23	195/25
Behavior aggressive	0/0	0/0	0/0	0/0	0/0	1/1	1/1
Convulsions – clonic	0/0	0/0	0/0	0/0	0/0	3/3	1/1
Licking excessive	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Prostration	0/0	0/0	0/0	1/1	0/0	125/23	186/25
Salivation	0/0	0/0	0/0	0/0	0/0	2/2	0/0
Skin*							
Hair sparse, lumbar	0/0	0/0	1/1	49/9	0/0	0/0	3/1
Hair absent, dorsal	0/0	0/0	0/0	36/4	0/0	0/0	0/0
Scabbed area, dorsal	0/0	0/0	0/0	127/15	12/2	39/7	137/13
Respiration							
Rapid breathing	0/0	0/0	0/0	0/0	0/0	121/23	156/25

* Only selected body regions are described here. The study report breaks down a large number of regions which were not deemed necessary to reproduce here.

Body weight (dams): Occasional decreases in body weight gain were observed following treatment with 10 mg/kg of the eutectic mixture of lidocaine/tetracaine during some of the internals. There were no test article related body weight or body weight gains noted at any dose levels in any group.

Food consumption (dams): There were no test-article related changes in maternal food consumption during gestation.

Toxicokinetics: Not completed in this study (see pilot study data).

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): Post-mortem necroscopic observations included scabbing and red discoloration at some of the injection sites in the 60 mg/kg/day lidocaine, 10 mg/kg/day tetracaine and the 10 mg/kg/day eutectic mixture of lidocaine and tetracaine. These findings were likely attributed to the test article.

There were no significant differences between groups in gravid uterine weights, adjusted Day 20 gestation body weights and body weight gains over Days 0-20.

There were no abortions or early deliveries noted, and pregnancy rate was similar across all groups (96-100%) except for the 5 mg/kg/day lidocaine group and the 5 mg/kg/day tetracaine group (84% and 88%, respectively). One female in the 60 mg/kg/day lidocaine group and one female in the 5 mg/kg/day lidocaine group had all resorptions, while all groups had 20 or more pregnant animals with viable fetuses.

Summary of Maternal and Developmental Observations at Uterine Examination							
Group	**Vehicle**	**Lidocaine**			**Tetracaine**		**Lido/Tet**
Dose (mg/kg)	**0**	**5**	**15**	**60**	**5**	**10**	**10/10**
Endpoint							
# Females on study	25	25	25	25	25	25	25
# not pregnant	0	4	0	1	3	0	1
# pregnant	25	21	25	24	22	25	24
Pregnancy Index (%)	100	84	100	96	88	100	96

# Died Pregnant	0	0	0	0	0	5	0
# Abortions	0	0	0	0	0	0	0
# Early deliveries	0	0	0	0	0	0	0
# Females with all resorptions	0	1	0	1	0	0	0
# females with viable fetuses Day 20 gestation	25	21	25	24	22	20	24
Mean Corpora Lutea	13.1	13.6	13.7	14.2	13.6	13.0	15.3*
Mean Implantation sites	12.3	12.3	12.7	12.7	12.5	12.3	12.3
Mean Preimplantation loss %	7.86	5.73	6.77	6.24	6.17	5.04	17.41
Mean Viable fetuses	11.6	11.8	12.2	12.0	12.0	11.6	11.9
Mean Fetal sex ratio (% males)	54.3	46.0	48.1	45.0	53.7	52.2	50.0
Mean postimplantation loss (%)	5.08	8.35	3.96	8.87	4.66	5.91	2.28
Mean Nonviable fetuses	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean Litter size	11.6	11.8	12.2	12.0	12.0	11.6	11.9
Mean Resorptions (early + late)	0.7	0.5	0.5	0.7	0.6	0.8	0.3
Mean Resorptions (early)	0.7	0.5	0.5	0.7	0.6	0.8	0.3
Mean Resorptions (late)	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* $p < 0.05$ compare to control

Offspring (malformations, variations, etc.): There were no significant differences in the mean fetal weights (males, females or combined) between treatment groups. Further, there were no differences in the incidence of external malformations or variations that could be attributed to drug treatment. There was a slight increase in the number of fetuses with unossified hyoid of the skull in the lidocaine/tetracaine eutectic mixture group; however, this was not statistically significant and within historical control range (maximum of 6.9% of fetuses and 24% litters affected).

Summary of Fetal External Observations
(Incidence expressed as the number of fetuses affected)

Group	Vehicle	Lidocaine			Tetracaine		Lido/Tet
Dose (mg/kg)	0	5	15	60	5	10	10/10
# of Litters Evaluated	25	20	25	23	22	20	24
# of Fetuses Evaluated	290	248	304	288	263	231	286
Body							
Entire, thoracogastroschisis	0	0	0	0	1	0	0
Forelimbs							
Digits, ectrodactyly	0	0	0	0	1	0	0
Hindlimbs							
Entire, abnormal flexure	0	0	0	0	1	0	0
Hind paw, edema	0	0	0	0	0	1	0
Tail							
Entire, absent	0	0	0	0	0	0	1
Summary of External Obs.							
Total Malformations							
# Litters (%)	0	0	0	0	1	0	1
# Fetuses (%)	0	0	0	0	1	0	1
Total Variations							
# Litters (%)	0	0	0	0	1	0	0
# Fetuses (%)	0	0	0	0	1	0	0

Summary of Fetal Visceral Observations
(Incidence expressed as the number of fetuses affected)

Group	Vehicle	Lidocaine	Tetracaine	Lido/Tet

Dose (mg/kg)	0	60	10	10/10
# of Litters Evaluated	24	23	20	24
# of Fetuses Evaluated	143	147	116	143
Kidney				
Increased renal pelvic cavitation	0	3	0	1
Ureter, dilated	0	1	0	0
Summary of Visceral Obs.				
Total Malformations				
# Litters (%)	0	0	0	0
# Fetuses (%)	0	0	0	0
Total Variations				
# Litters (%)	0	2	0	1
# Fetuses (%)	0	3	0	1

Summary of Fetal Skeletal Observations (Incidence expressed as the number of fetuses affected)				
Group	**Vehicle**	**Lidocaine**	**Tetracaine**	**Lido/Tet**
Dose (mg/kg)	**0**	**60**	**10**	**10/10**
# of Litters Evaluated	25	23	20	24
# of Fetuses Evaluated	147	141	115	143
Pelvic Girdle				
Ischium, incompletely ossified	0	1	1	0
Pubic, not ossified	1	0	0	0
Rib(s)				
Rib(s), bent	0	1	0	0
Rib(s), rudimentary	15	11	13	14
Rib(s), unilateral full rib	3	0	0	0
Skull				
Hyoid, not ossified	1	1	1	5
Sternum				
Sternebra(e), misaligned	1	2	1	1
Sternebra(e), not ossified	15	13	14	7
Summary of Skeletal Obs.				
Total Malformations				
# Litters (%)	0	0	0	0
# Fetuses (%)	0	0	0	0
Total Variations				
# Litters (%)	12	17	13	15
# Fetuses (%)	32	25	27	25

Study title: Study for Effects on Embryo-Fetal Development in New Zealand White Rabbits

Key study findings: The effect of subcutaneous lidocaine (1, 5 and 15 mg/kg/day), **tetracaine** (1 and 5 mg/kg/day) and the **eutectic combination** of the two (5 mg/kg/day each) on the embryo-fetal development of the rabbit were examined with the following key findings:

a. Maternal toxicity was noted at the high doses of lidocaine, tetracaine and the combination, indicating that the study is a valid assessment of the teratogenic potential of these drugs.

b. There was no evidence of teratogenicity in any treatment under the conditions of this assay.
c. The NOAEL for maternal toxicity was 1 mg/kg/day of tetracaine and 15 mg/kg/day of lidocaine. These doses correspond to 12 and 180 mg/m^2, on a body surface area basis.
d. The NOAEL for developmental effects was 5 mg/kg/day tetracaine, 15 mg/kg/day lidocaine and 5 mg/kg/day each in a eutectic mixture (highest dose tested). These doses correspond to 60, 180 and 60/60 mg/m^2, respectively, on a body surface area basis.

Study no.: 925-016
Volume #, and page #: Volume 6, Page 1
Conducting laboratory and location:

Date of study initiation: February 26, 2003
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Tetracaine base, Batch # 721724,
Lidocaine base, Lot # 811D0013

Methods

Doses: Lidocaine 1, 5 and 15 mg/kg, s.c.
Tetracaine 1 and 5 mg/kg, s.c.
Lidocaine/Tetracaine 5/5 mg/kg, s.c.

Species/strain: New Zealand White Hra(NZW)SPF Rabbits

Number/sex/group: 23/group as outlined in the table below:

Group Assignment		
Group Number	Dose Level (mg/kg/day)	Number of Time-mated Female Rabbits
1	0 (Vehicle Control)	23
2	1 (Lidocaine)	23
3	5 (Lidocaine)	23
4	15 (Lidocaine)	23
5	1 (Tetracaine)	23
6	5 (Tetracaine)	23
7	5/5 (Lidocaine/Tetracaine)	23

Route, formulation, volume, and infusion rate: Subcutaneous, vehicle was phosphate buffered saline, pH = 6.0 ± 0.2, volume of 1 ml/kg. The dosing formulations were determined to be stable for 14 days when refrigerated via preliminary studies.

Satellite groups used for toxicokinetics: Not completed in this study.

Study design: Test article and vehicle control administration began on Day 7 of gestation and continued through to include Day 20 of gestation. Individual doses were based on the most recent body weight. Test article/vehicle was administered via a 26-gauge hypodermic needle subcutaneously in the scapular and lumbar regions of the lower back. Dosing was alternate form left to right.

Parameters and endpoints evaluated:

Mortality and Clinical Signs: Animals were observed twice daily for morbidity, mortality, signs of injury and availability of food and water. Detailed clinical examinations were conducted daily from Days 7 through 29 of gestation.

Body Weights: Body weights were recorded on Days 0, 7, 10, 13, 16, 18, 21, 25 and 29 of gestation. Body weight changes were calculated for the following gestation day intervals: 0-7, 7-10, 10-13, 13-16, 16-18, 18-21, 21-29 and 0-29. Adjusted body weight (Day 29 gestation body weight minus gravid uterine weight) and adjusted body weight change (Days 0-29 of gestation) were also calculated.

Food Consumption: Food consumption was recorded daily and reported on the corresponding body weight days and calculated for the same intervals as body weight intervals.

Post Mortem Evaluations: On Day 29, dams were sacrificed by sodium pentobarbital injection followed by exsanguinations from the femoral blood vessels and immediately subjected to cesarean section. Maternal necropsy, ovarian and uterine examinations were completed. The following were recorded: gravid uterine weight, location of viable and nonviable fetuses, early and late resorptions, position of cervix, total number of implantations, number or corpora lutea on each ovary.

Teratogenic Examinations: Fetuses were individually weighed, sexed, tagged and examined for external malformations and variations. Fetuses were euthanized via intraperitoneal injection of sodium barbital. Approximately half were placed in Bouin's solution, the remaining in alcohol. Skeletal malformations and developmental variations were noted and classified as such under the supervision of a developmental toxicologist.

Statistical analysis: Statistical analysis was conducted according to the following table:

Statistical Analysis Methods	
Endpoint	**Analysis**
Parental In-life Data	
Gestation Body Weights	Group Pair-wise Comparisons
Gestation Body Weight Changes	Group Pair-wise Comparisons
Gestation Food Consumption	Group Pair-wise Comparisons
Adjusted Body Weights	Group Pair-wise Comparisons
Adjusted Body Weight Changes (Days 0-29)	Group Pair-wise Comparisons
Fertility Indices	
Pregnancy Index	Fisher's Exact Test
Uterine and Ovarian Exam	
Gravid Uterine Weights	Group Pair-wise Comparisons
Corpora Lutea/doe	Group Pair-wise Comparisons
Total Implantations/doe	Group Pair-wise Comparisons
Fetal Sex Ratio (% males/litter)	Fisher's Exact Test
Litter Size/doe	Group Pair-wise Comparisons
Viable Fetuses/doe	Group Pair-wise Comparisons
Nonviable Fetuses /doe	Descriptive Statistics
Total Number Resorptions/doe	Group Pair-wise Comparisons
Number Early Resorptions/doe	Group Pair-wise Comparisons
Number Late Resorptions/doe	Group Pair-wise Comparisons
% Preimplantation Loss (mean/doe)	Arcsin-Square-Root Transformation
% Postimplantation Loss (mean/doe)	Arcsin-Square-Root Transformation
Mean Fetal Body Weights	Covariate Analysis
Malformations by finding and exam type (external, visceral, and skeletal) – litter incidence[a]	Fisher's Exact Test
Variations by finding and exam type (external, visceral, and skeletal) – litter incidence[a]	Fisher's Exact Test
Total Malformations (external, visceral, and skeletal combined) – litter incidence[a]	Fisher's Exact Test
[a]Fetal and litter incidences are reported, but only the litter incidences were statistically analyzed.	

Results

Mortality (dams): One pregnant animal in the 5 mg/kg/day lidocaine group was sacrificed in extremis on Day 15 due to a hind limb impairment. This was not thought to be treatment-related. One pregnant animal in the 15 mg/kg/day lidocaine group was found dead on Day 21 and one pregnant animal in the 5 mg/kg/day tetracaine group was found dead on Day 17. The tetracaine animal had decreased activity, absence of feces and inappetance prior to death. There were no clinical signs in the 15 mg/kg/day lidocaine animal prior to death. The death of the animal in the tetracaine group was considered to be test-article related. However, the sponsor does not consider the death of the animals treated with lidocaine to be treatment-related. As dosing was completed on study day 20, this conclusion appears to be reasonable.

Clinical signs (dams): Lidocaine treatment-related clinical findings were limited to aggressive behavior in 2 dams treated with the high dose, hair absent/sparse in various regions and scabbed areas on the back that where likely related to injection sites irritation. Behavioral changes in the tetracaine treated animals included decreased activity, ataxia, aggressive behavior, convulsions and prostration. The tetracaine-induced prostration, ataxia

and to a lesser extent convulsions appear to have been increased by the addition of the lidocaine.

Summary of Clinical Observations in the Dams
(# times observed/total number of animals affected)

Group	Vehicle	Lidocaine			Tetracaine		Lido/Tet
N	23	23	23	23	23	23	23
Dose (mg/kg)	0	1	5	15	1	5	5/5
Behavior							
Activity Decreased	4/3	6/1	3/2	11/2	0/0	106/22	216/23
Activity Increased	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Ataxia	0/0	0/0	0/0	0/0	0/0	1/1	13/8
Behavior aggressive	0/0	0/0	0/0	0/0	0/0	13/1	10/1
Convulsions – clonic	0/0	0/0	0/0	0/0	0/0	12/9	18/11
Inappetence	0/0	0/0	0/0	0/0	0/0	2/1	0/0
Prostration	0/0	0/0	0/0	0/0	0/0	87/22	163/23
Skin*							
Hair sparse, lumbar	0/0	0/0	0/0	8/1	3/1	21/3	0/0
Hair absent, lumbar	1/1	3/1	0/0	15/2	3/1	0/0	0/0
Scabbed area, lumbar	0/0	0/0	0/0	23/2	25/2	64/7	10/1
Respiration							
Rapid breathing	0/0	0/0	0/0	0/0	0/0	102/21	219/23

* Only selected body regions are described here. The study report breaks down a large number of regions which were not deemed necessary to reproduce here.

Body weight (dams): There were no test-article related changes in body weight or body weight gain with any dose of lidocaine or with the low dose of tetracaine (1 mg/kg/day). Body weight and body weight gains of the dams in the 5 mg/kg/day tetracaine group and the 5/5 mg/kg/day lidocaine/tetracaine group were lower than the controls at the Day 7-21 gestational interval for tetracaine 5 mg/kg/day and the Day 0-29 gestational interval for the high dose tetracaine and lidocaine/tetracaine groups. These changes are considered to be treatment related.

Food consumption (dams): Food consumption in the lidocaine 15 mg/kg/day dams for gestational intervals Day 7-21 and Day 0-29 were slightly lower than controls, but not statistically significant. There as a statistically significant decrease in food consumption in dams treated with 5 mg/kg tetracaine or 5/5 mg/kg/day lidocaine/tetracaine for gestational intervals Day 7-21 and Day 0-29. These changes are considered to be treatment related.

Toxicokinetics: Not completed in this study (see pilot study data).

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): Post-mortem necroscopic observations included scabbing at the injection site in one 15 mg/kg/day lidocaine dam, 1 mg/kg/day tetracaine dam and 5 dams in the 5 mg/kg/day lidocaine/tetracaine group. Red discoloration at the injection sites were also noted in one 5 mg/kg/day tetracaine dam and 2 dams in the 5/5 mg/kg/day lidocaine/tetracaine group. These findings were likely attributed to the test article.

There were no abortions or any early deliveries noted in any group, and pregnancy rate was similar across all groups (91.3-100%). The number of females with viable litters was similar

across groups (ranged from 20-22). There were no statistically significant or toxicologically relevant changes in the number of corpora lutea, implantations, post-implantation loss, viable and non-viable fetuses or resorptions between groups.

Summary of Maternal and Developmental Observations at Uterine Examination							
Group	**Vehicle**	**Lidocaine**			**Tetracaine**		**Lido/Tet**
Dose (mg/kg)	**0**	**1**	**5**	**15**	**1**	**5**	**5/5**
Endpoint							
# Females on study	23	23	23	23	23	23	23
# not pregnant	1	2	2	2	2	0	1
# pregnant	22	21	21	21	21	23	22
Pregnancy Index (%)	95.7	91.3	91.3	91.3	91.3	100	95.7
# Died Pregnant	0	0	1	1	0	1	0
# Abortions	0	0	0	0	0	0	0
# Early deliveries	0	0	0	0	0	0	0
# Females with all resorptions	0	0	0	0	0	0	0
# females with viable fetuses Day 20 gestation	22	21	20	20	21	22	22
Mean Corpora Lutea	9.6	10.4	10.2	9.8	10.5	9.7	10.9
Mean Implantation sites	9.1	9.4	9.6	9.1	9.9	9.0	10.0
Mean Preimplantation loss %	5.21	10.61	5.42	7.34	5.93	6.36	6.42
Mean Viable fetuses	8.8	9.0	9.2	8.8	9.4	8.5	9.6
Mean Fetal sex ratio (% males)	54.1	56.7	49.6	51.4	49.8	46.8	52.8
Mean postimplantation loss (%)	2.66	3.0	3.47	2.69	4.16	5.79	3.89
Mean Nonviable fetuses	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mean Litter size	8.8	9.0	9.2	8.8	9.4	8.5	9.6
Mean Resorptions (early + late)	0.3	0.3	0.4	0.3	0.4	0.5	0.4
Mean Resorptions (early)	0.1	0.2	0.1	0.2	0.2	0.5	0.2
Mean Resorptions (late)	0.1	0.1	0.3	0.1	0.2	0.1	0.2

* $p < 0.05$ compare to control

Adjusted body weight and body weight gains were also not altered in dams treated with any regimen of lidocaine alone or 1 mg/kg tetracaine treatment. However, dams treated with 5 mg/kg/day tetracaine and 5/5 mg/kg/day lidocaine/tetracaine had a lower weight change from day 0 and animals in the 5/5 mg/kg/day lidocaine/tetracaine group had a lower adjusted bodyweight change from day 0 compared to control animals that was statistically significance. The magnitude of the body weight change from day 0 was approximately 28% for both the tetracaine and the tetracaine/lidocaine treatments, suggesting a primary role of tetracaine in this response.

Summary of Gravid Uterine Weight and Adjusted Body Weight Change Values							
Group	**Vehicle**	**Lidocaine**			**Tetracaine**		**Lido/Tet**
Dose (mg/kg)	**0**	**1**	**5**	**15**	**1**	**5**	**5/5**
Gravid uterine weight, kg	0.498	0.521	0.520	0.503	0.537	0.478	0.0875
Final body weight, kg	3.916	3.946	3.848	3.893	3.858	3.794	3.837
Adjusted final body weight, kg	3.418	3.425	3.328	3.389	3.321	3.318	3.323
Weight change from day 0, kg	0.538	0.540	0.515	0.519	0.477	0.390*	0.388*
Adjusted weight change from day 0, kg	0.041	0.019	-0.005	0.015	-0.060	-0.086	-0.126*

* $p < 0.05$ compared to vehicle-treated group

There were no significant differences in fetal body weight between treatment groups when examined as males, females or combined.

Offspring (malformations, variations, etc.): There were no statically significant increases in the total number of litters with **external malformations or external variations** noted under the conditions of the study. Statistical analysis of the data expressed on the basis of fetuses evaluated (rather than litters) was not completed by the sponsor. The data provided is reproduced below from the sponsor's Table 10.

Summary of Fetal External Observations (Incidence expressed as the number of fetuses affected)							
Group	**Vehicle**	**Lidocaine**			**Tetracaine**		**Lido/Tet**
Dose (mg/kg)	**0**	**1**	**5**	**15**	**1**	**5**	**5/5**
# of Litters Evaluated	22	21	20	20	21	22	22
# of Fetuses Evaluated	194	190	184	176	198	187	212
Body							
Abdomen, gastroschisis[1]	0	0	0	1	0	0	1
Entire, edema	0	0	0	0	0	0	1
Forelimbs							
Digits, ectrodactyly	0	0	0	0	0	0	1
Entire, abnormal flexure	0	0	0	0	0	0	1
Fore paw, abnormal flexure	0	1	0	0	0	0	1
Hind limb(s)							
Entire, abnormal flexure	0	0	0	0	0	0	1
Entire, malrotated	0	0	0	0	0	0	1
Tail							
Entire, absent	0	0	0	0	0	0	1
Summary of External Obs.							
Total Malformations							
# Litters (%)	0 (0)	0 (0)	0 (0)	1 (5.0)	0 (0)	0 (0)	2 (9.1)
# Fetuses (%)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)	2 (0.9)
Total Variations							
# Litters (%)	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9.1)
# Fetuses (%)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.9)

[1] Gastroschisis -A defect in the abdominal wall resulting from rupture of the amniotic membrane during physiological gut-loop herniation or, later, owing to delayed umbilical ring closure; usually accompanied by protrusion of viscera.

There were no statically significant increases in the total number of litters with **visceral malformations or visceral variations** noted under the conditions of the study. There were several rare malformations noted in a treatment group that were not seen in the concurrent controls not have they been seen in the sponsor's historical database for the facility. These include hydrocephaly (lateral ventricle), absent gallbladder, absent ureter / kidney, and smaller than normal ovary. Although rare, the sponsor noted that they occurred in only one or two animals and there were no other animals affected and therefore are not considered to be related to the test article. Statistical analysis of the data expressed on the basis of fetuses evaluated (rather than litters) was not completed by the sponsor. The absent gall bladder was also noted in one vehicle treated animal and therefore does not appear to be related to drug treatment. The absent kidney and ureter noted in the lidocaine:tetracaine group is not a common finding and was not detected in the historical control database (MARTA and MTA). However, as this finding occurs in only one animal, the evidence is rather weak that the effect could be attributed to the drug treatments.

Summary of Fetal Visceral Observations
Incidence expressed as the number of fetuses affected (%)

Group	Vehicle	Lidocaine			Tetracaine		Lido/Tet
Dose (mg/kg)	**0**	**1**	**5**	**15**	**1**	**5**	**5/5**
# of Litters Evaluated	22	21	20	20	21	22	22
# of Fetuses Evaluated	194	190	184	176	198	187	212
Gall Bladder							
Absent	1 (0.5)	2 (1.1)	0	1 (0.6)	0	0	0
Small	2 (1.0)	3 (1.6)	1 (0.5)	2 (1.1)	2 (1.0)	3 (1.6)	10 (4.7)
Kidney							
absent	0	0	0	0	0	0	1 (0.5)
Liver							
nodule	0	0	0	0	1 (0.5)	0	0
Ovary							
smaller than normal	0	0	0	0	0	1 (0.5)	0
Ureter							
Absent	0	0	0	0	0	0	1 (0.5)
Brain							
Lat ventricle, hydrocephaly	0	0	0	0	0	1 (0.5)	0
Head							
Eye, microphthalmia	0	0	0	0	0	0	1 (0.5)
Aortic arch							
Dilated	0	1 (0.5)	1 (0.5)	0	1 (0.5)	0	1 (0.5)
Lungs (both)							
Smaller than normal	0	0	0	0	0	1 (0.5)	0
Diaphragm							
Diaphramatic hernia	0	0	0	0	0	1 (0.5)	0
Intraventricular septum							
Discontinuous	0	1 (0.5)	1 (0.5)	0	1 (0.5)	0	0
Pulmonary truck							
Constricted	0	1 (0.5)	0	0	0	0	1 (0.5)
Lung, Right							
Azygous lobe absent	9 (4.6)	8 (4.2)	13 (7.1)	2 (1.1)	0	6 (3.2)	6 (2.8)
Subclavian Artery							
Retroesophageal	0	1 (0.5)	0	0	0	0	0
Thoracic Cavity							
Fluid Filled	0	0	0	0	0	0	1 (0.5)
Persistent truncus arteriosus	0	0	0	0	1 (0.5)	0	0
Summary of Visceral Obs.							

Total Malformations							
# Litters (%)	1 (4.5)	2 (9.5)	1 (5.0)	1 (5.0)	2 (9.5)	2 (9.1)	2 (9.1)
# Fetuses (%)	1 (0.5)	3 (1.6)	1 (0.5)	1 (0.6)	2 (1.0)	2 (1.1)	3 (1.4)
Total Variations							
# Litters (%)	6 (27.3)	8 (38.1)	8 (40.0)	4 (20.0)	2 (9.5)	8 (36.4)	9 (40.9)
# Fetuses (%)	10 (5.2)	11 (5.8)	14 (7.6)	4 (2.3)	2 (1.0)	9 (4.8)	14 (6.6)

There were no statistically significant increases in the total number of **skeletal malformations or variations** when examined on a litter basis. Statistical analysis on the basis of the number of fetuses examined was not completed by the sponsor. The table below reproduces the data in sponsor's table 11. Although there were several malformations noted which exceeded the incidence in the control group, these were not statistically significant. The incidence of most of these observations were within the historic control range for the laboratory or occurred in a single pup at a single dose group and therefore considered by the sponsor to be unrelated to the study drug. One fetus displayed multiple external and skeletal malformations, including sacral neural arches absent, fused or misaligned for sacral vertebrae, sternebrae absent, thoracic centra absent and/or fused and thoracic neural arches misaligned and/or misshapen. As these findings were in a single pup, not statistically significant and/or were within the historical control range, the sponsor does not consider them to be related to the test article.

Summary of Fetal Skeletal Observations
Incidence expressed as the number of fetuses affected (%)

Group	Vehicle	Lidocaine	Tetracaine	Lido/Tet
Dose (mg/kg)	**0**	**15**	**5**	**5/5**
# of Litters Evaluated	22	20	22	22
# of Fetuses Evaluated	194	176	187	212
Caudal vertebra(e)				
Neural arch(es) absent	0	0	0	1 (0.5)
Cervical vertebra(e)				
Centra, additional ossification	1 (0.5)	0	0	3 1.4)
Centra, misshapen	0	0	0	3 (1.4)
Neural arch(es), additional ossific.	4 (2.1)	0	5 (2.7)	5 (2.4)
Neural arch(es), misaligned	0	0	0	1 (0.5)
Neural arch(es), misshapen	0	0	0	1 (0.5)
Hindlimb				
Talus, not ossified	0	0	0	2 (0.9)
Rib(s)				
Rib(s), discontinuous	1 (0.5)	0	0	1 (0.5)
Rib(s), fused	0	0	0	1 (0.5)
Rib(s), rudimentary	50 (25.8)	48 (27.3)	53 (28.3)	60 (28.3)
Rib(s), unilateral fill rib	28 (14.4)	26 (14.8)	20 (10.7)	34 (16.0)
Sacral Vertebra(e)				
Neural arch(es), absent	0	0	0	1 (0.5)
Neural arch(es), fused	0	0	0	1 (0.5)
Neural arch(es), misaligned	0	0	0	1 (0.5)
Skull				
Frontal bone, additional ossific.	0	0	3 (1.6)	1 (0.5)
Hyoid arch, bent	9 (4.6)	11 (6.3)	7 (3.7)	8 (3.8)
Hyoid body, not ossified	1 (0.5)	2 (1.1)	0	3 (1.4)
Nasal bone, additional ossific.	0	0	0	1 (0.5)
Sternum				
Sternebra(e), absent	0	0	0	1 (0.5)

Sternebra(e), additional ossific.	4 (2.1)	6 (3.4)	3 (1.6)	2 (0.9)
Sternebra(e), fused	2 (1.0)	6 (3.4)	2 (1.1)	2 (0.9)
Sternebra(e), misaligned	2 (1.0)	1 (0.6)	0	0
Sternebra(e), not ossified	16 (8.2)	16 (9.1)	20 (10.7)	32 (15.1)
Thoracic vertebra(e)				
Centra, absent	0	0	0	1 (0.5)
Centra, fused	0	0	0	1 (0.5)
Neural arch(es), misaligned	0	0	0	1 (0.5)
Neural arch(es), misshapen	0	0	0	1 (0.5)
Summary of Skeletal Obs.				
Total Malformations				
# Litters (%)	3 (13.6)	5 (25)	2 (9.1)	5 (22.7)
# Fetuses (%)	3 (1.5)	6 (3.4)	2 (1.1)	7 (3.3)
Total Variations				
# Litters (%)	22 (100)	20 (100)	20 (90.9)	22 (100)
# Fetuses (%)	80 (41.2)	80 (45.4)	78 (41.7)	99 (46.7)

Closer inspection of the individual fetus findings for the rare abnormalities noted above, indicates that fetus 9 from dam 346 who was treated with 5 /5 mg/kd lidocaine/tetracaine presented with the following malformations and variations:

Malformations and Variations in Fetus 9 from Dam 346 (lidocaine/tetracaine treatment group)			
Area	**Location**	**Classification**	**Observation**
External Observations			
Body	Abdomen	Malformation	Gastroschisis
Forelimb(s)	Digits	Malformation	Ectrodactyly
Forelimb(s)	Entire	Variation	Abnormal flexure
Hind limb(s)	Entire	Variation	Abnormal flexure
Hind limb(s)	Entire	Malformation	Malrotate
Tail	Entire	Malformation	Absent
Visceral Observations			
Abdominal cavity	Gallbladder	Variation	Smaller than normal
Abdominal cavity	Kidney	Malformation	Absent
Abdominal cavity	Ureter	Malformation	Absent
Skeletal Observations			
Thoracic vertebra(e)	Centra	Malformation	Absent
Thoracic vertebra(e)	Centra	Malformation	Fused
Skull	Hyoid body	Variation	Not ossified
Caudal vertebra(e)	Neural arch(es)	Malformation	Absent
Sacral vertebra(e)	Neural arch(es)	Malformation	Absent
Sacral vertebra(e)	Neural arch(es)	Malformation	Fused
Sacral vertebra(e)	Neural arch(es)	Malformation	Misaligned
Thoracic vertebra(e)	Neural arch(es)	Malformation	Misaligned
Thoracic vertebra(e)	Neural arch(es)	Malformation	Misshapen
Ribs	Ribs	Malformation	Fused
Sternum	Sternebra(e)	Variation	Absent
Sternum	Sternebra(e)	Variation	Not ossified
Hind limb(s)	talus	Variation	Not ossified

Dam 346 had a low final body weight and adjusted final body weight 2.964 kg. In addition, fetus 9 was approximately 15 grams less mass than the other 10 fetuses in the litter and clearly stands out from the remainder of the fetuses. Collectively, these data are not consistent with a teratogenic effect of lidocaine or tetracaine. The evidence for material toxicity in this Dam is a more likely explanation of the fetal effects noted for a good sized litter. This reviewer does not feel that the finding is related to the drug-treatment.

Prenatal and postnatal development

Study Title: Study for toxic effects on pre- and postnatal development, including maternal function, in rats

Key study findings: **Tetracaine base** administration to the female rat from GD6 to LD20 resulted in the following key findings:

- Mortality: 2 dams at a dose of 2.5 mg/kg and 1 dam at a dose of 7.5 mg/kg during gestation
- Clinical observations (maternal): decreased activity, ataxia, prostration, rapid breathing, and scabs at injection site at a dose of 7.5 mg/kg
- Body weight gains: decreased at a dose of 7.5 mg/kg during gestation and in all treated groups during LD0-4
- No developmental affects on offspring when tetracaine base was given s.c.
- NOAEL = [F_0] 2.5 mg/kg/day (based on observations and body weight gains) [F_1] 7.5 mg/kg/day

Study no: 925-017
Volume #, and page #: 22, pp. 22-1
Conducting laboratory and location: [redacted]
Date of study initiation: 28 March 2003
GLP compliance/QA report: Yes (X) No ( )
Drug, lot #, radiolabel, and % purity: tetracaine base/Z-02-003/purity not specified on CofA
Formulation/vehicle: sterile water containing NaH_2PO_4 and Na_2HPO_4

Methods:

Species/strain: timed-mated Sprague Dawley rats – CD(SD)IGS BR, [redacted]
Doses employed: 0.75, 2.5, 7.5 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left should and lumbar regions)
Study design: GD6-LD20
Number/sex/group: 25/group
Parameters and endpoints evaluated: Time-mated rats were used for the study. Clinical observations (twice daily), body weight, food consumption, parturition and litter observations, culling of litters to 8/sex on LD4, pup developmental indices during lactation included static righting reflex, pinna detachment, cliff aversion, eye opening, air drop righting reflex, auditory startle (end of lactation period), and during development vaginal opening, preputial separation, motor activity (PD 35) and step-through passive avoidance (PD74-77). F1 pups were allowed to mate and a cesarean section was performed on GD13 and male animals were euthanized after completion of the cesarean section.

Observation times and results:

Observations	**Results**
Mortality (maternal)	Two dams were found dead on GD 17 and 19 at a dose of

	2.5 mg/kg, and 1 dam was found dead on GD17 at a dose of 7.5 mg/kg. Cause of death was not determined. All other maternal animals survived to scheduled euthanasia.
Body weights (maternal)	Body weights were unremarkable for gestation and lactation. Body weight gains were decreased on GD6-10 (10%) and GD17-20 (12%) at a dose of 7.5 mg/kg. Body weight gains were decreased in all treated groups during LD0-4 (24-59%), and were statistically significantly decreased for the entire lactation period (LD0-21, 24%) at a dose of 0.75 mg/kg.
Food consumption (maternal)	Unremarkable during gestation and lactation.
F_0 In-life observations	
Dams	Decreased activity, ataxia, prostration, rapid breathing, and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the gestation and lactation periods. Delivery/littering data were unremarkable.
Offspring	A low incidence of desquamation (entire body) at a dose of 7.5 mg/kg, and scabbed in all dose groups were observed.
F_0 Terminal/necroscopic evaluations	
Dams	Discoloration, scabs, and skin thickening were observed at a dose of 7.5 mg/kg.
Offspring	Unremarkable.
F_1 In-life observations	
Male and female rats	Unremarkable for observations, developmental landmarks, and post-weaning behavioral tests. It should be noted that there were statistically significant increases in motor activity and time to achieve passive avoidance at doses $\geq$ 2.5 mg/kg. The reason for the statistical significance is that the control group animals in this study exhibited values that were outside (below) the historical control data (HCD), while the treated group values are within HCD.
Dams	Unremarkable.
Body weights	
Male rats	Unremarkable.
Female rats	Unremarkable.

Terminal/necroscopic evaluations
Male rats Unremarkable.
Dams Unremarkable.
[Note: GD = gestation day; LD=lactation day; PD=postnatal day]

2.6.6.7 Local tolerance:

A. Study title: A dermal irritation study of S-Caine™ (lidocaine 7% and tetracaine 7% cream) peel in rabbits.

Key study findings:
- Very slight erythema and edema with S-Caine™ Peel by 48 hrs with resolution by 72 hrs
- TK: animals were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: 925-018
Volume #, and page #: 14, pp. 14-1
Conducting laboratory and location: [redacted]
Date of study initiation: 23 July 2003
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/PE-1806; [redacted] % for lidocaine, [redacted] for tetracaine
Formulation/vehicle: Placebo Peel/ PE-1908; mineral oil/020269

Doses: 6 grams on 2 inches squared (or 30 cm^2) for 2 hours applied as a single application
Study design: Rabbits (N=3 male) were topically administered S-Caine™ Peel for 2 hrs. The peel was then removed; the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 0, 24, 48, and 72 hrs. TK samples were taken at 2, 3, 6, 12, and 24 hrs after application. Body weights were recorded on SD1 and animals were euthanized 72 hrs after application.

Results: A 2 hour administration of S-Caine™ Peel was well tolerated. Very slight erythema was observed in both the placebo and S-Caine™ Peel groups, but the S-Caine™ Peel group also exhibited very slight edema.

		Study interval (hrs)[a]			
Treatment	**Severity**	**0**	**24**	**48**	**72**
Placebo Peel	**Erythema**				
	1=very slight	2/3	---	---	---
S-Caine™ Peel	**Erythema**				
	1=very slight	1/3	---	---	---
	Edema				
	1=very slight			1/3	

[a] number represents number affected/sample size.

Toxicokinetics: All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine (17-fold and 14-fold, respectively), but the T_{max} was comparable (3-6 hrs). T_{max} for both lidocaine and tetracaine occurred after peel removal, indicating a 're-distribution' from the skin to the systemic exposure. There was high intervariability in the C_{max} and AUC for lidocaine and tetracaine, with the highest variability being observed for tetracaine.

APPENDIX B: Pharmacokinetic Parameters for Lidocaine and Tetracaine for Individual Rabbits

	Lidocaine			Tetracaine		
Animal No.	7141	7142	7143	7141	7142	7143
C_{max} (ng/mL)	149.14	89.41	305.31	13.08	2.73	22.03
T_{max} (hr)	6	3	3	6	3	3
AUC_{0-24} (ng•hr/mL)	1,693	316	1,056	120.7	5.5	54.8
Dose (mg)	420	420	420	420	420	420
$NAUC_{0-24}$ (ng•hr/mL/mg)	4.03	0.75	2.51	0.287	0.013	0.130
r^2	0.9919	***0.5436***	1.0000	NC	NC	NC
k_e (hr^{-1})	0.1571	***0.0840***	0.1443	NC	NC	NC
$t_{1/2}$ (hr)	4.4	***8.2***	4.8	NC	NC	NC

NC = Could not be calculated by WinNonlin

Note: The values in bold italics are considered unreliable since r^2 for the fit was < 0.8, and the values are not included in the mean values for k_e and $t_{1/2}$.

B. Study title: Modified primary dermal irritation.

Key study findings:

- S-Caine™ Peel was mildly irritating
- TK: Rabbits were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: X9L313G
Volume #, and page #: 14, pp. 14-64
Conducting laboratory and location: [redacted]
Date of study initiation: 10 January 2000
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/SP 12-29-99A/purity not specified
Formulation/vehicle: Placebo Peel/ SP 12-29-99 placebo; mineral oil
Doses: 6 grams on 2 inches squared (or 30 cm^2) for 2 hrs applied as a single application using a hill top chamber

Study design: Rabbits (N=6 male) were topically administered S-Caine™ Peel for 2 hrs. The peel was then removed, the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 0, 24, 48, and 72 hrs. TK samples were taken at 0, 2, and 3 hrs after application. Body weights were recorded prior to dosing.

Results: The primary irritation score (MPI) for the mineral oil, placebo peel, and S-Caine™ Peel were 0.2, 0.2, and 0.3, respectively. The MPI scores indicate that all treatments were mildly irritating to the skin, but the S-Caine™ Peel had a higher incidence of erythema than the other groups.

		Study interval (hrs)[a]					
Treatment	**Severity**	**0**	**2**	**12**	**24**	**48**	**72**
Mineral oil	**Erythema, very slight**	3/6	2/6	2/6	2/6		1/6
Placebo Peel	**Erythema, very slight**	2/6	1/6	1/6	1/6	1/6	1/6
	Edema, very slight			1/6			
S-Caine™ Peel	**Erythema, very slight**	4/6	2/6	2/6	2/6	2/6	2/6

[a] number represents number affected/sample size.

Toxicokinetics: The level of detection for lidocaine and tetracaine were 100 ng/mL and 5 ng/mL, respectively. All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine (6.6-fold and 8-fold, respectively), but the T_{max} was comparable. One problem with the TK study is that exposure levels were only examined through 3 hrs post-dose, therefore, making it difficult to know the complete AUC and the true $t_{1/2}$ of the drugs.

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Table 2. Pharmacokinetic Parameters for Lidocaine and Tetracaine in Male Rabbits After a 2-Hour Application of S-Caine™ Peel

	Lidocaine			Tetracaine		
Rabbit No.	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-3} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-3} (ng•hr/mL)
25035	190	3	260	25	3	33.5
25037	240	3	315	64	3	63.5
25059	140	3	235	29	3	41.5
25060	170	3	250	10	3	14.0
25061	160	3	305	23	3	44.5
25068	210	2	400	18	3	21.8
Mean ± SD	185 ± 36	2.8 ± 0.4	294 ± 61	28.2 ± 18.7	3.0 0.0	36.5 17.6

C. Study title: Dermal absorption and dermal irritation study of S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream) in neonatal piglets.

Key study findings:

- No irritation was observed with S-Caine™ Peel
- TK: animals were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: 925-005
Volume #, and page #: 14, pp. 14-89
Conducting laboratory and location:
Date of study initiation: 06 September 2002
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/PE-1806/ % for lidocaine and tetracaine
Formulation/vehicle: mineral oil/lot no. 001191
Doses: 5 grams on 100 cm^2 for 30 mins, 10 grams on 100 cm^2 for 60 mins
Study design: Neonatal piglets (N=3/sex/group) were topically administered S-Caine™ Peel as outlined above. The peel was then removed, the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 1, 24, 48, and 72 hrs. TK samples were taken at 0, 30, 60, 90 mins, and 2, 4, 8, 12, and 24 hrs after application. Body weights were recorded prior to dosing, on the day of dosing, and study termination. Animals were euthanized 72 hrs after dosing and microscopic evaluation of the skin was conducted.

Results: No dermal irritation was observed, body weights, clinical observations, and microscopic evaluations were unremarkable.

Toxicokinetics: All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine for all treated groups. Ratios for the 5g/30 min group for C_{max} and AUC for male piglets were 10-fold and 168-fold, respectively, and for female piglets were 81-fold and 194-fold, respectively. Female piglets had higher exposure to lidocaine and tetracaine than male piglets in the 5 g/30 min group. T_{max} for the 5g/30 min group was longer for the male piglets for lidocaine, but were comparable for tetracaine for both genders. Ratios for the 10g/60 min group for C_{max} and AUC were comparable for male and female piglets (94-98-fold and 121-148-fold, respectively). T_{max} was also comparable for the 10g/60 min group. T_{max} tended to occur after patch removal, indicated a possible depot affect in the skin or a 're-distribution' of the lidocaine and tetracaine from the skin to the whole body. T_{max} was not dependent on dose, application time, or gender.

Table 2. Mean Pharmacokinetic Parameters for Neonatal Piglets Receiving S-Caine™ Peel Topically

Parameter	Male Piglets				Female Piglets			
	Lidocaine		Tetracaine		Lidocaine		Tetracaine	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
Group 1: 30-Minute Application of 5 g								
C_{max} (ng/mL)	645 ± 219	3	6.49 ± 1.58	3	590 ± 213	3	7.26 ± 1.75	3
T_{max} (hr)	6.7 ± 2.3	3	2.2 ± 1.6	3	4.0 ± 0.0	3	1.5 ± 0.5	3
AUC_{0-24} (ng•hr/mL)	8,881 ± 1,914	3	52.9 ± 8.5	3	7,655 ± 2,473	3	39.3 ± 18.0	3
k_e (hr^{-1})	0.1174 ± 0.0082	3	0.1302 ± 0.0296	3	0.1254 ± 0.0298	3	0.1267	1
$t_{1/2}$ (hr)	5.9 ± 0.4	3	5.5 ± 1.3	3	5.7 ± 1.2	3	5.5	1
$AUC_{0-\infty}$ (ng•hr/mL)	9,696 ± 1,993	3	61.1 ± 8.4	3	8,209 ± 2,529	3	60.3	1
Weight (kg)	1.96 ± 0.18	3	1.96 ± 0.18	3	2.06 ± 0.21	3	2.06 ± 0.21	3
C_{max}/Wt (ng/mL/kg)	335 ± 137	3	3.33 ± 0.90	3	295 ± 135	3	3.61 ± 1.23	3
AUC_{0-24}/Wt (ng•hr/mL/kg)	4,594 ± 1,340	3	26.9 ± 3.3	3	3,765 ± 1,457	3	19.6 ± 10.6	3
Group 2: 60-Minute Application of 10 g								
C_{max} (ng/mL)	1,618 ± 382	3	16.42 ± 7.20	3	1,277 ± 159	3	13.64 ± 5.67	3
T_{max} (hr)	4.0 ± 0.0	3	2.5 ± 1.3	3	3.3 ± 1.2	3	4.0 ± 0.0	3
AUC_{0-24} (ng•hr/mL)	21,550 ± 6,746	3	145.4 ± 24.2	3	18,675 ± 5,364	3	154.4 ± 74.9	3
k_e (hr^{-1})	0.1065 ± 0.0087	3	0.1433 ± 0.0506	3	0.1158 ± 0.0394	3	0.1262	2
$t_{1/2}$ (hr)	6.5 ± 0.6	3	5.4 ± 2.4	3	6.4 ± 2.0	3	5.9	2
$AUC_{0-\infty}$ (ng•hr/mL)	24,051 ± 7,540	3	153.4 ± 29.8	3	21,038 ± 6,894	3	143.5	2
Weight (kg)	2.03 ± 0.15	3	2.03 ± 0.15	3	1.97 ± 0.17	3	1.97 ± 0.17	3
C_{max}/Wt (ng/mL/kg)	792 ± 136	3	8.05 ± 3.20	3	648 ± 58	3	6.80 ± 2.31	3
AUC_{0-24}/Wt (ng•hr/mL/kg)	10,492 ± 2,570	3	71.3 ± 6.7	3	9,417 ± 2,378	3	77.0 ± 34.9	3

Note: Standard deviations were not calculated for n < 3.

2.6.6.8 Special toxicology studies:

A. Study title: Phototoxicity tests in rabbits.

Key study findings:

- The adequacy of the study is questionable as inadequate control groups were employed.
- However, 1 out of 4 sites that were irradiated after S-Caine Peel application showed well-defined/moderately severe erythema and slight-moderate edema.

Study no.: 0432LZ03.001
Volume #, and page #: 14, 14-190 (Original NDA Application)
Conducting laboratory and location: [redacted]
Date of study initiation: 24 October 2003
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel/PE01806/ [redacted] % for lidocaine and tetracaine
Formulation/vehicle: NA; positive control of 0.5% 8-MOPS
Doses: 0.2 mL on 4 cm^2 site
Study design: Rabbits (N=3/sex/group) were used. Group 1 was treated with mineral oil, positive control, or S-Caine™ Peel for 15 mins, then the skin was irradiated at to non-erythemogenic (i.e, uV greater than 280 nm or ~163 joules, cm^2) at a distance of 10 inches for 60 mins. After the irradiation, the peel was removed and Draize scoring was performed. Group 2 was irradiated for 60 mins as outlined above, the mineral oil, positive control, or S-Caine™ Peel was applied and allowed to dry for 15 mins. All treatments remained in place for 60 mins, after which they were removed and Draize scoring was performed. An untreated site was also included on each animal. Draize scoring was performed at 24, 48, 72, and 96 hrs after treatment completion.

Results:
One out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. No other affects were observed. The adequacy of the study is questionable as there are study design confounds which include: 1) the absorption spectrum of the product is unknown; 2) the correct control groups were not included; and 3) it is unknown if the stratum corneum is affected by removal of the peel. The absorption spectrum information is important because I cannot confirm that the wavelength used in the study (erythemogenic - uV greater than 280 nm or ~163 joules, cm^2) is the wavelength that should have been used in the study. The wavelength to use in these studies depends on what wavelengths are absorbed by the drug. If the drug product does not absorb between 290 and 700 nm then phototoxicity is not likely to be a safety concern, but without the information on the absorption spectrum the interpretation of the study results is that S-Caine™ Peel treatment may cause irritation at the site of application if exposed to sunlight.

Dermal Observations/Post Treatment

	24 Hours															
Rabbit	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2*	2*	0	0	3	2	0	0	1*	0	0	0	0	0	0	0
1329♂	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0
1331♀	1*	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
mean	0.5	0.3	0.0	0.0	2.7	2.8	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.8	0.0	0.0	0.5	0.4	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	48 Hours															
Rabbit	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2*	1*	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1331♀	1*	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
mean	0.5	0.2	0.0	0.0	2.8	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.4	0.0	0.0	0.4	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

ER = erythema
ED = edema
♂ = Male
♀ = Female
Sites 1 & 2 = Test article
Sites 3 & 4 = Vehicle
Sites 5 & 6 = Positive control (8-MOP)
Sites 7 & 8 =Untreated
Sites 1, 3, 5 and 7 (left side) irradiated after treatment
Sites 2, 4, 6 and 8 (right side) irradiated prior to treatment

*This score is attributed to mechanical damage occurring during test material removal after treatment and light exposure. Difficulty was experienced in test article removal in all six animals after treatment (test article/light exposure).

Dermal Observations/Post Treatment

Rabbit No.	72 Hours															
	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2A*	0	0	0	3	1	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1331♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
Mean	0.3	0.0	0	0	3.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rabbit No.	96 Hours															
	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2A*	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1331♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
Mean	0.3	0.0	0.0	0.0	2.8	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.0	0.0	0.0	0.4	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

ER = erythema
ED = edema
A = 1/3 of area of test area
♂ = Male
♀ = Female

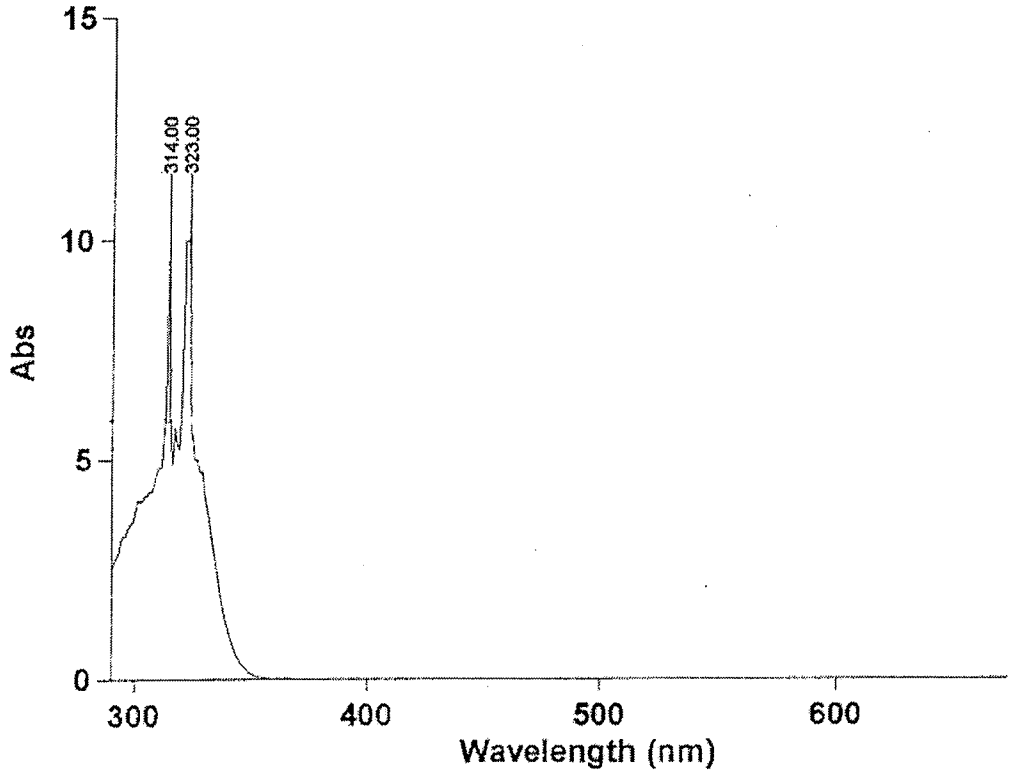
Sites 1 & 2 = Test article
Sites 3 & 4 = Vehicle
Sites 5 & 6 = Positive control (8-MOP)
Sites 7 & 8 =Untreated

Sites 1, 3, 5 and 7 (left side) irradiated after treatment
Sites 2, 4, 6 and 8 (right side) irradiated prior to treatment

*This score is attributed to mechanical damage occurring during test material removal after treatment and light exposure. Difficulty was experienced in test article removal in all six animals after treatment (test article/light exposure).

The control groups used in the study are inadequate. The Sponsor conducted the study with an untreated control and an ethanol control. No placebo peel was included, therefore, it is difficult to determine if the one reaction was a result of the active ingredients or the peel components themselves. A more adequately designed study should have included sites that were treated with drug only (no light), vehicle (with and without light) or light only. The group in the study that was irradiated and then had the S-Caine™ Peel applied is an inadequate control because if the drug has any anti-inflammatory effect it might mask the erythema and edema even when applied after the light.

The absorption spectrum received from the Sponsor (below) indicates that the peel absorbs light ~312-314 nm range.



The Sponsor indicates that no phototoxicity was conducted with the S-Caine™ Peel placebo. In this light, it is difficult to determine if the reaction was a result of components in the peel or a result of the active components.

The affect of the peel on the stratum corneum is unknown, but according to the Sponsor there is no evidence that layers of the epithelium are removed when then peel is removed.

2.6.6.9 Discussion and Conclusions:

The sponsor conducted a standard fertility and reproductive toxicity and a pre- and postnatal development study in rats with tetracaine base at doses up to 7.5 mg/kg. Clinical observations in both studies were decreased activity, prostration, rapid breathing, and scabs at the injection site at a dose of 7.5 mg/kg. In the pre- and postnatal development study, 3 dams (2 dams at a dose of 2.5 mg/kg, 1 dam at a dose of 7.5 mg/kg) were found dead during gestation. The cause of death in these three animals is not known, however, due to the lack of a clear dose-relationship, these deaths do not appear to be attributable to the tetracaine. Body weight gains were decreased in the fertility study in male rats at a dose of 7.5 mg/kg during the entire treatment period, decreased in female rats in all treated groups during premating, and at a dose of 7.5 mg/kg during GD0-7. Body weight gains were also decreased in the pre- and postnatal development study during gestation at a dose of 7.5 mg/kg and in

all treated groups during LD0-4. There were no affects of tetracaine base on male or female fertility or pre- and postnatal development.

S-Caine™ Peel (7% lidocaine, 7% tetracaine) was found to produce mild irritation in rabbits, but did not cause any irritation in neonatal piglets. In all animal species examined lidocaine > tetracaine for exposure and there was a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal.

Experimental shortcomings in the phototoxicity study make it difficult to interpret, but 1 out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. The results of the test indicate a possibility of a phototoxic reaction if treated skin is exposed to sun light as the absorption spectrum indicates S-Caine™ Peel absorbs light in the 312-314 nm range.

2.6.6.10 Tables and Figures:

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Unresolved toxicology issues: There are two unresolved issues which are discussed below:

1) In light of the problems with the current phototoxicity study regarding the lack of appropriate controls, the unknown affect of the peel on the stratum corneum, and the observation that human subjects in the clinical trials that lidocaine may be present in the body for up to 24 hrs (no data are available for tetracaine as it was not detected) there is a safety concern regarding the possible photo-irritation at the application site. It is unclear if the stratum corneum is removed when the peel is removed, although the Sponsor indicates that there is no evidence from the clinical trials that it is removed. It should be noted that a specific study was not conducted to address the removal of the stratum corneum when the peel is removed. In this light, if the stratum corneum is removed, either partially or completely, then it is probable that the skin with be sensitive to sun, not as a result of the drug's light absorption or photochemical properties, but as a result of physical disruption of the skin's integrity. This concern regarding photo-irritation can be adequately addressed in product labeling and will not require any further non-clinical testing.

2) Eye irritation was not assessed in non-clinical or clinical trials. While there is no indication that the components or active ingredients, lidocaine and tetracaine, of the S-Caine™ Peel cause eye irritation, the potential of the active ingredients, lidocaine and tetracaine, to anesthetize the eyelid is highly likely if they are contacted by the S-Caine™ Peel. This concern regarding eye toxicity can be adequately addressed in

product labeling and will not require any further non-clinical testing. The Sponsor [redacted] in their proposed label.

Recommendations: The NDA may be approved with minor alterations to the proposed label.

Suggested labeling: NOTE: The multiples of exposure that are included in the label are low because many of the doses utilized in the non-clinical studies were below the doses topically administered in humans when comparing the surface area and exposed area (cm^2). However, the low multiples of exposure do not offer a significant safety risk with S-Caine Peel because there is low or no systemic exposure of lidocaine and tetracaine after dermal application. A non-teratogenic effects section was added to the label following receipt of a consult for the Pregnancy Labeling Team (PLT). The articles cited by the PLT were reviewed and the section appropriately revised to provide more details on the reported findings to assistant in future labeling of the current and future products. The proposed labeling received from the sponsor was identical to the approved Synera™ labeling. However, the multiples of exposure for the S-Caine Peel are not the same as those of the S-Caine Patch (Synera™) and therefore must be updated for this drug product. The Sponsor's proposed labeling is reproduced below:

(Note: strike-through indicates corrections to proposed label, blue text indicate insertions/edits to the proposed label):

Proposed Labeling (EDR May 25, 2006)	**Reviewer Comments / Recommendations**
PRECAUTIONS	**The following text should be included in the precautions section of the label:** [redacted]
Carcinogenesis, Mutagenesis, Impairment of Fertility:	
Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.	No changes are required.
Mutagenesis: The mutagenic potential of lidocaine base and tetracaine base has been determined in the in vitro Ames Bacterial Reverse Mutation Assay, the in vitro chromosome aberration assay using Chinese hamster ovary cells, and the in vivo mouse micronucleus assay. Lidocaine was negative in all three assays. Tetracaine was negative in the in vitro Ames assay and the in vivo mouse micronucleus assay. In the in vitro chromosome aberration assay, tetracaine was negative in the absence of metabolic activation, and equivocal in the presence of metabolic activation.	Comment: The text is identical to the approved Synera product labeling. No changes are required.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Reviewer Signature: R. Daniel Mellon, Ph.D.
Pharmacology Toxicology Supervisor, DAARP

APPENDIX/ATTACHMENTS

Reference List

Alexson SE, Diczfalusy M, Halldin M and Swedmark S (2002) Involvement of liver carboxylesterases in the in vitro metabolism of lidocaine. *Drug Metab Dispos* **30**:643-647.

de Jong RH and Bonin JD (1980) Deaths from local anesthetic-induced convulsions in mice. *Anesth Analg* **59**:401-405.

Elvin AT, Cole AF, Pieper JA, Rolbin SH and Lalka D (1981) Effect of food on lidocaine kinetics: mechanism of food-related alteration in high intrinsic clearance drug elimination. *Clin Pharmacol Ther* **30**:455-460.

Fujinaga M and Mazze RI (1986) Reproductive and teratogenic effects of lidocaine in Sprague-Dawley rats. *Anesthesiology* **65**:626-632.

Hino Y, Inoue H, Kudo K, Nishida N and Ikeda N (2001) Distribution of tetracaine and its metabolite in rabbits after high versus normal spinal anesthesia. *Forensic Sci Int* **124**:130-136.

Moore PA (1999) Adverse drug interactions in dental practice: interactions associated with local anesthetics, sedatives and anxiolytics. Part IV of a series. *J Am Dent Assoc* **130**:541-554.

National Toxicology Program (1990) NTP Toxicology and Carcinogenesis Studies of 2,6-Xylidine (2,6-Dimethylaniline) (CAS No. 87-62-7) in Charles River CD Rats (Feed Studies). *Natl Toxicol Program Tech Rep Ser* **278**:1-138.

Rowland M, Thomson PD, Guichard A and Melmon KL (1971) Disposition kinetics of lidocaine in normal subjects. *Ann N Y Acad Sci* **179**:383-398.

Smith RF, Kurkjian MF, Mattran KM and Kurtz SL (1989) Behavioral effects of prenatal exposure to lidocaine in the rat: effects of dosage and of gestational age at administration. *Neurotoxicol Teratol* **11**:395-403.

Smith RF, Wharton GG, Kurtz SL, Mattran KM and Hollenbeck AR (1986) Behavioral effects of mid-pregnancy administration of lidocaine and mepivacaine in the rat. *Neurobehav Toxicol Teratol* **8**:61-68.

Thomson PD, Rowland M and Melmon KL (1971) The influence of heart failure, liver disease, and renal failure on the disposition of lidocaine in man. *Am Heart J* **82**:417-421.

Wilcox KM, Rowlett JK, Paul IA, Ordway GA and Woolverton WL (2000) On the relationship between the dopamine transporter and the reinforcing effects of local anesthetics in rhesus monkeys: practical and theoretical concerns. *Psychopharmacology (Berl)* **153**:139-147.

Zito RA and Reid PR (1981) Lidocaine kinetics: relationships between early lidocaine kinetics and indocyanine green clearance. *J Clin Pharmacol* **21**:100-105.

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/s/

R. Daniel Mellon
6/14/2006 11:33:07 PM
PHARMACOLOGIST
Pharmacology Toxicology Supervisor, DAARP

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-717**
SERIAL NUMBER:	**N000**
DATE RECEIVED BY CENTER:	**11/17/2003**
DRUG NAME:	**7% lidocaine/7% tetracaine (S-Caine™ peel)**
INDICATION:	**local dermal anesthesia on intact skin**
SPONSOR:	**Zars, Inc.**
DOCUMENTS REVIEWED:	**18 of 102 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Pratibha Rana**

Date of review submission to Division File System (DFS): 03 September 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling.
Note: The multiples of exposure that are included in the label are low because many of the doses utilized in the non-clinical studies were below the doses topically administered in humans when comparing the surface area and exposed area (cm^2). However, the low multiples of exposure do not offer a significant safety risk with TetraPeel because there is low or no systemic exposure of lidocaine and tetracaine after dermal application. A non-teratogenic effects section was added to the label following receipt of a consult for the Pregnancy Labeling Team (PLT). The articles cited by the PLT were reviewed and the section appropriately revised to provide more details on the reported findings to assistant in future labeling of the current and future products.

PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.

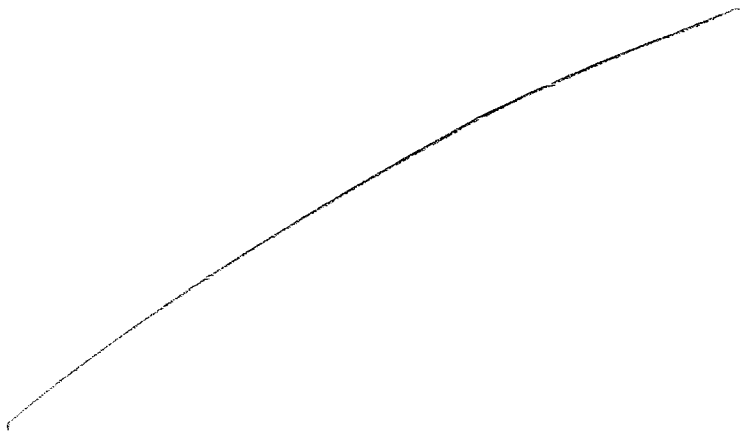
Mutagenesis: The mutagenic potential of lidocaine base and tetracaine base has been determined in the *in vitro* Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames and the *in vivo* mouse micronucleus assays. In the *in vitro* chromosomal aberration assay tetracaine was negative in the absence of metabolic activation, and equivocal in the presence of metabolic activation.

Impairment of Fertility: Lidocaine did not affect fertility in female rats when

Use in Pregnancy:

Teratogenic Effects: Pregnancy Category B. Lidocaine was not

Nonteratogenic Effects. Lidocaine, contained 1:100.000 epinephrine at a



II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No affects of tetracaine base on male or female fertility or pre- and postnatal development were observed. S-Caine™ Peel (7% lidocaine, 7% tetracaine) was found to produce mild irritation in rabbits, but did not cause any irritation in neonatal piglets. In all animal species examined lidocaine > tetracaine for exposure and there was a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal. Experimental shortcomings in the

phototoxicity study make it difficult to interpret, but 1 out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. The results of the test indicate a possibility of a phototoxic reaction if the treated skin is exposed to sun light as the absorption spectrum indicates S-Caine™ Peel absorbs light in the 312-314 nm range.

B. Pharmacologic activity
Both lidocaine (amide-linked) and tetracaine (para-aminobenzoic acid ester) are local anesthetics which have similar pharmacological profiles and are about equipotent. Local anesthetics block nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na+ channels. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na+ channels.

C. Nonclinical safety issues relevant to clinical use
In light of the problems with the current phototoxicity study regarding the lack of appropriate controls, the unknown affect of the peel on the stratum corneum, and the observation that human subjects in the clinical trials that lidocaine may be present in the body for up to 24 hrs (no data is available for tetracaine as it was not detected) there is a safety concern regarding the possible photo-irritation at the application site. It is unclear if the stratum corneum is removed when the peel is removed, although the Sponsor indicates that there is no evidence from the clinical trials that it is removed. It should be noted that a specific study was not conducted to address the removal of the stratum corneum when the peel is removed. In this light, if the stratum corneum is removed, either partially or completely, then it is probable that the skin with be sensitive to sun, not as a result of the drug's light absorption or photochemical properties, but as a result of physical disruption of the skin's integrity. This concern of photo-irritation can be adequately addressed in product labeling and will not require any further non-clinical testing. Eye irritation is also a concern and it can be handled in the label. The Sponsor [redacted] in their proposed label.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

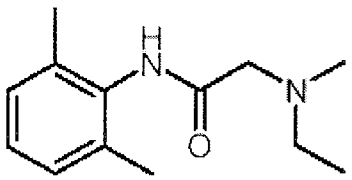
TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

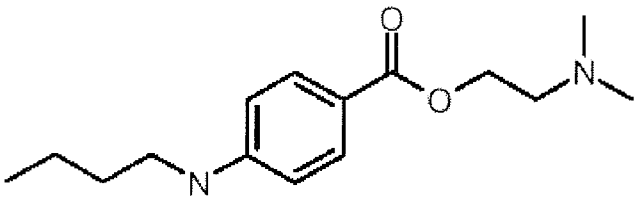
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-717
REVIEW NUMBER:	1
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/17 November 2003/AZ
INFORMATION TO SPONSOR:	Yes ( ) No (X)
SPONSOR:	Zars, Inc. 1142 West 2320 Soute, Suite A Salt Lake City, UT 84119
MANUFACTURER FOR DRUG SUBSTANCE :	[lidocaine] [tetracaine]
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DACCADP
HFD #:	170
REVIEW COMPLETION DATE:	26 August 2004
DRUG:	
TRADE NAME:	S-Caine™ Peel
GENERIC NAME (LIST ALPHABETICALLY):	lidocaine/tetracaine
CODE NAME:	NA
CHEMICAL NAME:	
[lidocaine] 2-(Diethylamino)-N-(2,6-dimethylphenyl)-acetamide	
[tetracaine] 2-(Dimethylamino)ethyl p-(butylamino)benzoate	
CAS REGISTRY NUMBER:	[lidocaine] 137-58-6 [tetracaine] 94-24-6
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	
	[lidocaine] $C_{14}H_{22}N_2O$/234.3 [tetracaine] $C_{15}H_{24}N_2O_2$/264.41

STRUCTURE:



Lidocaine



Tetracaine

RELEVANT INDS/NDAS/DMFS:	IND 58,823/NDA 21-623 (S-Caine Patch) IND 59,801 (S-Caine™ Peel)
DRUG CLASS:	Local anesthetics of the amide type (lidocaine) and ester type (tetracaine).

INTENDED CLINICAL POPULATION: local dermal anesthesia on intact skin

ROUTE OF ADMINISTRATION: topical

FORMULATION:

Component	Function
Lidocaine, USP	Active, Anesthetic Agent
Tetracaine, USP	Active, Anesthetic Agent
Dibasic Calcium Phosphate, Anhydrous, USP	
Purified Water, USP	
Polyvinyl Alcohol, USP	
Petrolatum, USP	
Sorbitan Monopalmitate, NF	
Methylparaben, NF	
Propylparaben, NF	

The excipients in the above formulation can be found in approved drug products at equal or greater levels and therefore do not pose any unique toxicological concerns.

BACKGROUND: The Sponsor has submitted a 505(b)(2) NDA application for S-Caine™ Peel which is a 1:1 eutectic mixture of lidocaine and tetracaine. The majority of the information to support this NDA is derived from the Sponsor's for S-Caine™ Patch NDA (21-623). In the current NDA the Sponsor submitted analytical data for toxicokinetic analyses, Fertilty/Reproduction and Pre- and postnatal development reproductive toxicity studies for tetracaine base, and dermal irritation and absorption studies for the S-Caine™ Peel. As previously agreed the Sponsor has referenced the 28-day dermal toxicity study with the S-Caine™ Patch in rabbits to support the S-Caine™ Peel. The 28-day study was previously reviewed under the S-Caine™ Patch NDA and findings included skin irritation, histological changes of epidermal surface exudates, epidermal necrosis, acute dermatitis, trace to moderate epithelial hyperplasia and fibrosis of the dermis, but no difference in gender, abraded or non-abraded sites for exposure.

Two degradation products are found in the S-Caine™ Peel, The Sponsor has established specifications of respectively. Tetracaine *in vivo* is metabolized via hydrolysis by plasma esterases to both of these degradation products. The specifications established for these degradation products are below the levels normally found in the plasma when tetracaine is administered. These degradation products were also detected in the S-Caine™ Patch NDA. It should also be noted that the Sponsor There are no toxicology issues with the established specifications for these degradation products.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-717 are owned by Astra Zeneca or are data for which Zars, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-717 that Zars, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Zars, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-717.

Studies reviewed within this submission:

Study Title	Study no.	Volume	Page
Report for ——— study: 30G-1PA final report, sample analysis of tetracaine and lidocaine in rabbit plasma by gas chromatography with nitrogen phosphorus detection	X91313G	9	9-3
Analysis of tetracaine and lidocaine in rabbit plasma by LC/MS/MS	67GC	9	9-23
Analysis of tetracaine and lidocaine in porcine plasma by LC/MS/MS	68G-1P	9	9-86
Final report for analysis of lidocaine in rat plasma by LC/MS/MS	67G-1P	9	9-190
Final report for analysis of lidocaine in rat plasma by LS/MS/MS	68GB	10	10-1
Final report for analysis of tetracaine and lidocaine in rabbit plasma by LC/MS/MS	67GB	10	10-81
Method validation report, analytical method GL-LID-01, lidocaine and tetracaine in human plasma by LC/MS/MS	---	10	10-181
A dermal irritation study of S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream) in rabbits	925-018	14	14-1
Modified primary dermal irritation	X9L313G	14	14-64
Toxicokinetic report for modified primary dermal irritation test	X9L313G	14	14-80
Dermal absorption and dermal irritation study of S-Caine ™ Peel (lidocaine 7% and tetracaine 7% cream) in neonatal piglets	925-005	14	14-89
Phototoxicity test in rabbits	0432LZ03.001	14	14-190
A study to assess the effects of fertility and early embryonic development to implantation in rats	925-014	17	17-1
Study for toxic effects on pre- and postnatal development, including maternal function, in rats	925-017	22	22-1

Studies not reviewed within this submission (previously reviewed):

Study Title	Study no.	NDA/IND
Acute Toxicology/Dermal Irritation		
Modified Primary Skin Irritation (Rabbits).	X9C009G	N21-623
A dermal irritation study of S-Caine™ Patch in rabbits	925-002	N21-623
Dermal Sensitization – Buehler Method	X9C010G	I58,823
Repeat Dose Toxicology		
A 28 day dermal toxicity study of S-Caine™ Patch in rabbits	925-004	N21-623
Genotoxicity		
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with lidocaine base	23840-0-409OECD	N21-623
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with tetracaine base	23841-0-409OECD	N21-623
Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with lidocaine base	23840-0-437OECD	N21-623
Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with tetracaine base	23841-0-437OECD	N21-623
In vivo mouse micronucleus assay with lidocaine base	23840-0-455OECD	N21-623
In vivo mouse micronucleus assay with tetracaine base	23841-0-455OECD	N21-623
Reproductive Toxicology		
Pilot Study for effects on embryo-fetal development in rats	925-012	N21-623
Pilot prenatal development toxicity study in New Zealand white rabbits	925-013	N21-623
Final toxicology report for study 925-015, Study for effects on embryo-fetal development in rats	925-015	N21-623
Final toxicology report for study 925-016; Study for effects on embryo-fetal development in rabbits	925-016	N21-623

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new studies were submitted for review.

Genetic toxicology: The genotoxic potential of lidocaine base and tetracaine base were determined in the *in vitro* Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosome aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus assay. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames assay and the *in vivo* mouse micronucleus assay. Tetracaine was negative in the absence of metabolic activation in the *in vitro* CHO chromosomal aberration assay, and equivocal in the presence of metabolic activation.

Carcinogenicity: No new studies were submitted for review.

Reproductive toxicology: Tetracaine base did affect male or female fertility or pre- and postnatal development in rats when administered s.c. up to a dose of 2.5 mg/kg/day.

Special toxicology: S-Caine™ Peel was mildly irritating to rabbits. Experimental shortcomings in the phototoxicity study make it difficult to interpret, but 1 out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. The results of the test indicate a possibility of a phototoxic reaction if the treated skin is exposed to sun light and the absorption spectrum indicates S-Caine™ Peel absorbs light in the 312-314 nm range.

2.6.6.2 Single-dose toxicity: No new studies were submitted for review.

2.6.6.3 Repeat-dose toxicity: No new studies were submitted for review.

2.6.6.4 Genetic toxicology: No new studies were submitted for review.

2.6.6.5 Carcinogenicity: No new studies were submitted for review.

2.6.6.6 Reproductive and developmental toxicology:

A. Study Title: A study to assess the effects of fertility and early embryonic development to implantation in rats.

Key study findings: Tetracaine base administration to both the male and female rat resulted in the following key findings:

- Clinical observations: decreased activity, prostration, rapid breathing, and scabs at injection site in male and female rats at a dose of 7.5 mg/kg
- Body weight gains: decreased in male rats at a dose of 7.5 mg/kg during the entire treatment period; decreased in female rats in all treated groups during premating, and at a dose of 7.5 mg/kg during GD 0-7
- Organ weights: decrease in prostate weights and an increase in ovary weights at a dose of 7.5 mg/kg
- No effect on male or female fertility when tetracaine base was given s.c.
- NOAEL (general)= 2.5 mg/kg/day for male and female rats (based on observations and body weight gains)
- NOAEL (fertility)=7.5 mg/kg/day for male and female rats

Study no: 925-014
Volume #, and page #: 17, pp. 17-1
Conducting laboratory and location:
Date of study initiation: 28 March 2003
GLP compliance/QA report: Yes (X) No ( )

Drug, lot #, radiolabel, and % purity: tetracaine base/Z-02-003/purity not specified on CoA
Formulation/vehicle: sterile water containing NaH_2PO_4 and Na_2HPO_4

Methods:

Species/strain: Sprague Dawley rats — CD(SD)IGS BR, [redacted]
Doses employed: 0.75, 2.5, 7.5 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left shoulder and lumbar regions)
Study design: daily dosing, [males] 28 days premating, 14-21 days mating, through GD7; [females] 14 days premating, 14-21 days mating, through GD7
Number/sex/group: 25/sex/group
Parameters and endpoints evaluated: [male rats] clinical observations twice daily; body weights were recorded every 3-4 days, and food consumption was recorded weekly; gross pathology, terminal body weights, testes, epididymis, seminal vesicle, and prostate organs were weighted, sperm analysis was conducted; [female rats] clinical observations twice daily, body weights and food consumption were recorded every 4 days during the pre-mating and mating periods and on GD 0, 4, 7, 10, 13; cesarean section on GD 13 with standard parameters collected, gravid uterine and ovaries/cervix were weighed

Observation times and results:

Observations	**Results**
Male rats	
Mortality	All animals survived to scheduled euthanasia.
Clinical signs	Decreased activity, ataxia, prostration, rapid breathing, hair absent or sparse and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the premating, mating, and postmating periods.
Body weights	Body weights were statistically significantly decreased (5-9%) beginning on SD22 (premating period) and continuing through postmating at a dose of 7.5 mg/kg. Also at 7.5 mg/kg body weight gains were decreased for the premating, mating, and postmating periods (14%, 30%, and 17%, respectively).
Food consumption	Statistically significantly decreased at a dose of 7.5 mg/kg during the premating period (SW3-9, 9-10%), and during the postmating period (SW 9-10, 12%).
Terminal/necroscopic evaluations	Unremarkable.
Organ weights	Terminal body weight was statistically significantly decreased (9%) and prostate weight was decreased (13%) at a dose of 7.5 mg/kg.
Reproductive/fertility Indices	Unremarkable.

Sperm analysis	Unremarkable.
Female rats	
Mortality	One died at a dose of 7.5 mg/kg on SD16 30 mins after dosing. Cause of death was not determined. All other animals survived to scheduled euthanasia.
Female rats	
Clinical signs	Decreased activity, prostration, rapid breathing, and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the premating, mating, and gestation periods.
Body weights	Body weights were statistically significantly decreased on SD15 (premating, 4%), and on GD 7-13 (3-6%) at a dose of 7.5 mg/kg. Body weight gains were decreased during the premating period on SD4-8 in all doses (18-31%), SD11-15 at doses ≥2.5 mg/kg (18-29%), and SD 1-15 for all doses (11-21%, statistically significant at doses ≥2.5 mg/kg. Body weight gains were decreased at a dose of 7.5 mg/kg during GD0-4 (19%, statistically significant), and GD4-7 (24%), GD0-7 (21%, statistically significant).
Food consumption	Unremarkable during premating and gestation.
Terminal/necroscopic evaluations	Unremarkable.
Organ weights	Ovary weight was increased (43%) at a dose of 7.5 mg/kg. Uterus/cervix weight was increased (16%) at a dose of 2.5 mg/kg.
Reproductive/fertility Indices	Estrous cyclicity was normal for the length and number of cycles. Unremarkable for fertility indices.
Cesarean section data	Unremarkable.

[Note: GD = gestation day; SD=study day; SW=study week]

B. Study Title: Study for toxic effects on pre- and postnatal development, including maternal function, in rats

Key study findings: Tetracaine base administration to the female rat from GD6 to LD20 resulted in the following key findings:

- Mortality: 2 dams at a dose of 2.5 mg/kg and 1 dam at a dose of 7.5 mg/kg during gestation
- Clinical observations (maternal): decreased activity, ataxia, prostration, rapid breathing, and scabs at injection site at a dose of 7.5 mg/kg

- Body weight gains: decreased at a dose of 7.5 mg/kg during gestation and in all treated groups during LD 0-4
- No developmental affects on offspring when tetracaine base was given s.c.
- NOAEL = [F_0] 2.5 mg/kg/day (based on observations and body weight gains) [F_1] 7.5 mg/kg/day

Study no: 925-017
Volume #, and page #: 22, pp. 22-1
Conducting laboratory and location: [redacted]
Date of study initiation: 28 March 2003
GLP compliance/QA report: Yes (X) No ( )
Drug, lot #, radiolabel, and % purity: tetracaine base/Z-02-003/purity not specified on CofA
Formulation/vehicle: sterile water containing NaH_2PO_4 and Na_2HPO_4

Methods:

Species/strain: timed-mated Sprague Dawley rats — CD(SD)IGS BR, [redacted]
Doses employed: 0.75, 2.5, 7.5 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left should and lumbar regions)
Study design: GD6-LD20
Number/sex/group: 25/group
Parameters and endpoints evaluated: Time-mated rats were used for the study. Clinical observations (twice daily), body weight, food consumption, parturition and litter observations, culling of litters to 8/sex on LD4, pup developmental indices during lactation included static righting reflex, pinna detachment, cliff aversion, eye opening, air drop righting reflex, auditory startle (end of lactation period), and during development vaginal opening, preputial separation, motor activity (PD 35) and step-through passive avoidance (PD74-77). F1 pups were allowed to mate and a cesarean section was performed on GD13 and male animals were euthanized after completion of the cesarean section.

Observation times and results:

Observations	**Results**
Mortality (maternal)	Two dams were found dead on GD 17 and 19 at a dose of 2.5 mg/kg, and 1 dam was found dead on GD17 at a dose of 7.5 mg/kg. Cause of death was not determined. All other maternal animals survived to scheduled euthanasia.
Body weights (maternal)	Body weights were unremarkable for gestation and lactation. Body weight gains were decreased on GD 6-10 (10%) and GD17-20 (12%) at a dose of 7.5 mg/kg. Body weight gains were decreased in all treated groups during LD0-4 (24-59%), and were statistically significantly decreased for the entire lactation period (LD0-21, 24%) at a dose of 0.75 mg/kg.
Food consumption (maternal)	Unremarkable during gestation and lactation.

F_0
In-life observations

Dams	Decreased activity, ataxia, prostration, rapid breathing, and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the gestation and lactation periods. Delivery/littering data were unremarkable.
Offspring	A low incidence of desquamation (entire body) at a dose of 7.5 mg/kg, and scabbed in all dose groups were observed.

F_0
Terminal/necroscopic evaluations

Dams	Discoloration, scabs, and skin thickening were observed at a dose of 7.5 mg/kg.
Offspring	Unremarkable.

F_1
In-life observations

Male and female rats	Unremarkable for observations, developmental landmarks, and post-weaning behavioral tests. It should be noted that there were statistically significant increases in motor activity and time to achieve passive avoidance at doses $\geq$ 2.5 mg/kg. The reason for the statistical significance is that the control group animals in this study exhibited values that were outside (below) the historical control data (HCD), while the treated group values are within HCD.
Dams	Unremarkable.

Body weights

Male rats	Unremarkable.
Female rats	Unremarkable.

Terminal/necroscopic evaluations

Male rats	Unremarkable.
Dams	Unremarkable.

[Note: GD = gestation day; LD=lactation day; PD=postnatal day]

2.6.6.7 Local tolerance:

A. Study title: A dermal irritation study of S-Caine™ (lidocaine 7% and tetracaine 7% cream) peel in rabbits.

Key study findings:

- Very slight erythema and edema with S-Caine™ Peel by 48 hrs with resolution by 72 hrs
- TK: animals were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: 925-018
Volume #, and page #: 14, pp. 14-1
Conducting laboratory and location: [redacted]
Date of study initiation: 23 July 2003
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/PE-1806 [redacted]% for lidocaine, [redacted]% for tetracaine
Formulation/vehicle: Placebo Peel/ PE-1908; mineral oil/020269

Doses: 6 grams on 2 inches squared (or 30 cm^2) for 2 hours applied as a single application
Study design: Rabbits (N=3 male) were topically administered S-Caine™ Peel for 2 hrs. The peel was then removed; the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 0, 24, 48, and 72 hrs. TK samples were taken at 2, 3, 6, 12, and 24 hrs after application. Body weights were recorded on SD1 and animals were euthanized 72 hrs after application.

Results: A 2 hour administration of S-Caine™ Peel was well tolerated. Very slight erythema was observed in both the placebo and S-Caine™ Peel groups, but the S-Caine™ Peel group also exhibited very slight edema.

		Study interval (hrs)[a]			
Treatment	**Severity**	**0**	**24**	**48**	**72**
Placebo Peel	**Erythema**				
	1=very slight	2/3	---	---	---
S-Caine™ Peel	**Erythema**				
	1=very slight	1/3	---	---	---
	Edema				
	1=very slight			1/3	

[a] number represents number affected/sample size.

Toxicokinetics: All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine (17-fold and 14-fold, respectively), but the T_{max} was comparable (3-6 hrs). T_{max} for both lidocaine and tetracaine occurred after peel removal indicating a 're-distribution' from the skin to the systemic exposure. There was high intervariability in the C_{max} and AUC for lidocaine and tetracaine, with the highest variability being observed for tetracaine.

APPENDIX B: Pharmacokinetic Parameters for Lidocaine and Tetracaine for Individual Rabbits

	Lidocaine			Tetracaine		
Animal No.	7141	7142	7143	7141	7142	7143
C_{max} (ng/mL)	149.14	89.41	305.31	13.08	2.73	22.03
T_{max} (hr)	6	3	3	6	3	3
AUC_{0-24} (ng•hr/mL)	1,693	316	1,056	120.7	5.5	54.8
Dose (mg)	420	420	420	420	420	420
$NAUC_{0-24}$ (ng•hr/mL/mg)	4.03	0.75	2.51	0.287	0.013	0.130
r^2	0.9919	***0.5436***	1.0000	NC	NC	NC
k_e (hr^{-1})	0.1571	***0.0840***	0.1443	NC	NC	NC
$t_{1/2}$ (hr)	4.4	***8.2***	4.8	NC	NC	NC

NC = Could not be calculated by WinNonlin

Note: The values in bold italics are considered unreliable since r^2 for the fit was < 0.8, and the values are not included in the mean values for k_e and $t_{1/2}$.

B. Study title: Modified primary dermal irritation.

Key study findings:

- S-Caine™ Peel was mildly irritating
- TK: Rabbits were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: X9L313G
Volume #, and page #: 14, pp. 14-64
Conducting laboratory and location:
Date of study initiation: 10 January 2000
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/SP 12-29-99A/purity not specified
Formulation/vehicle: Placebo Peel/ SP 12-29-99 placebo; mineral oil
Doses: 6 grams on 2 inches squared (or 30 cm^2) for 2 hrs applied as a single application using a hill top chamber
Study design: Rabbits (N=6 male) were topically administered S-Caine™ Peel for 2 hrs. The peel was then removed, the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 0, 24, 48, and 72 hrs. TK samples were taken at 0, 2, and 3 hrs after application. Body weights were recorded prior to dosing.

Results: The primary irritation score (MPI) for the mineral oil, placebo peel, and S-Caine™ Peel were 0.2, 0.2, and 0.3, respectively. The MPI scores indicate that all treatments were mildly irritating to the skin, but the S-Caine™ Peel had a higher incidence of erythema than the other groups.

		Study interval (hrs)[a]					
Treatment	**Severity**	**0**	**2**	**12**	**24**	**48**	**72**
Mineral oil	**Erythema, very slight**	3/6	2/6	2/6	2/6		1/6
Placebo Peel	**Erythema, very slight**	2/6	1/6	1/6	1/6	1/6	1/6
	Edema, very slight			1/6			
S-Caine™ Peel	**Erythema, very slight**	4/6	2/6	2/6	2/6	2/6	2/6

[a] number represents number affected/sample size.

Toxicokinetics: The level of detection for lidocaine and tetracaine were 100 ng/mL and 5 ng/mL, respectively. All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine (6.6-fold and 8-fold, respectively), but the T_{max} was comparable. One problem with the TK study is that exposure levels were only examined through 3 hrs post-dose, therefore, making it difficult to know the complete AUC and the true $t_{1/2}$ of the drugs.

Table 2. Pharmacokinetic Parameters for Lidocaine and Tetracaine in Male Rabbits After a 2-Hour Application of S-Caine™ Peel

	Lidocaine			Tetracaine		
Rabbit No.	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-3} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-3} (ng•hr/mL)
25035	190	3	260	25	3	33.5
25037	240	3	315	64	3	63.5
25059	140	3	235	29	3	41.5
25060	170	3	250	10	3	14.0
25061	160	3	305	23	3	44.5
25068	210	2	400	18	3	21.8
Mean ± SD	185 ± 36	2.8 ± 0.4	294 ± 61	28.2 ± 18.7	3.0 0.0	36.5 17.6

C. Study title: Dermal absorption and dermal irritation study of S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream) in neonatal piglets.

Key study findings:

- No irritation was observed with S-Caine™ Peel
- TK: animals were exposed to lidocaine > tetracaine with a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal

Study no.: 925-005
Volume #, and page #: 14, pp. 14-89
Conducting laboratory and location: [redacted]
Date of study initiation: 06 September 2002
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel (7% lidocaine, 7% tetracaine)/PE-1806/ — % for lidocaine and tetracaine
Formulation/vehicle: mineral oil/lot no. 001191
Doses: 5 grams on 100 cm^2 for 30 mins, 10 grams on 100 cm^2 for 60 mins
Study design: Neonatal piglets (N=3/sex/group) were topically administered S-Caine™ Peel as outlined above. The peel was then removed, the area cleaned with a water and a cloth, and then dermal irritation using Draize scoring was conducted at times of 1, 24, 48, and 72 hrs. TK samples were taken at 0, 30, 60, 90 mins, and 2, 4, 8, 12, and 24 hrs after application. Body weights were recorded prior to dosing, on the day of dosing, and study termination. Animals were euthanized 72 hrs after dosing and microscopic evaluation of the skin was conducted.

Results: No dermal irritation was observed, body weights, clinical observations, and microscopic evaluations were unremarkable.

Toxicokinetics: All plasma samples had detectable levels of lidocaine and tetracaine. C_{max} and AUC values were higher for lidocaine than tetracaine for all treated groups. Ratios for the 5g/30 min group for C_{max} and AUC for male piglets were 10-fold and 168-fold, respectively, and for female piglets were 81-fold and 194-fold, respectively. Female piglets had higher exposure to lidocaine and tetracaine than male piglets in the 5 g/30 min group. T_{max} for the 5g/30 min group was longer for the male piglets for lidocaine, but were comparable for tetracaine for both genders. Ratios for the 10g/60 min group for C_{max} and AUC were comparable for male and female piglets (94-98-fold and 121-148-fold, respectively). T_{max} was also comparable for the 10g/60 min group. T_{max} tended to occur after patch removal, indicated a possible depot affect in the skin or a 're-distribution' of the lidocaine and tetracaine from the skin to the whole body. T_{max} was not dependent on dose, application time, or gender.

Table 2 Mean Pharmacokinetic Parameters for Neonatal Piglets Receiving S-Caine™ Peel Topically

Parameter	Male Piglets				Female Piglets			
	Lidocaine		Tetracaine		Lidocaine		Tetracaine	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
Group 1: 30-Minute Application of 5 g								
C_{max} (ng/mL)	645 ± 219	3	5.49 ± 1.58	3	590 ± 213	3	7.26 ± 1.76	3
T_{max} (hr)	6.7 ± 2.3	3	2.2 ± 1.6	3	4.3 ± 3.0	3	1.5 ± 0.5	3
AUC_{0-24} (ng•hr/mL)	8,881 ± 1,914	3	52.9 ± 8.5	3	7,655 ± 2,473	3	39.8 ± 18.0	3
k_e (hr^{-1})	0.1174 ± 0.0062	3	0.1302 ± 0.0296	3	0.1254 ± 0.0298	3	0.1267	1
$t_{1/2}$ (hr)	5.9 ± 0.4	3	5.5 ± 1.3	3	5.7 ± 1.2	3	5.5	1
$AUC_{0-\infty}$ (ng•hr/mL)	9,696 ± 1,998	3	61.1 ± 8.4	3	8,209 ± 2,529	3	60.3	1
Weight (kg)	1.96 ± 0.18	3	1.95 ± 0.18	3	2.06 ± 0.21	3	2.06 ± 0.21	3
C_{max}/Wt (ng/mL/kg)	335 ± 137	3	3.33 ± 0.90	3	296 ± 135	3	3.61 ± 1.23	3
AUC_{0-24}/Wt (ng•hr/mL/kg)	4,534 ± 1,340	3	26.9 ± 3.3	3	3,785 ± 1,457	3	19.6 ± 10.6	3
Group 2: 60-Minute Application of 10 g								
C_{max} (ng/mL)	1,618 ± 382	3	16.42 ± 7.28	3	1,277 ± 159	3	13.64 ± 5.67	3
T_{max} (hr)	4.0 ± 0.0	3	2.5 ± 1.3	3	3.3 ± 1.2	3	4.0 ± 0.0	3
AUC_{0-24} (ng•hr/mL)	21,550 ± 6,745	3	145.4 ± 24.2	3	18,675 ± 5,364	3	154.4 ± 74.9	3
k_e (hr^{-1})	0.1065 ± 0.0087	3	0.1439 ± 0.0506	3	0.1158 ± 0.0094	3	0.1262	2
$t_{1/2}$ (hr)	6.5 ± 0.6	3	5.4 ± 2.4	3	6.4 ± 2.0	3	5.9	2
$AUC_{0-\infty}$ (ng•hr/mL)	24,051 ± 7,540	3	153.4 ± 39.6	3	21,038 ± 6,894	3	143.5	2
Weight (kg)	2.03 ± 0.16	3	2.03 ± 0.15	3	1.97 ± 0.17	3	1.97 ± 0.17	3
C_{max}/Wt (ng/mL/kg)	792 ± 136	3	8.06 ± 3.20	3	648 ± 68	3	6.80 ± 2.31	3
AUC_{0-24}/Wt (ng•hr/mL/kg)	10,492 ± 2,570	3	71.3 ± 6.7	3	9,417 ± 2,378	3	77.0 ± 34.9	3

Note: Standard deviations were not calculated for n < 3.

2.6.6.8 Special toxicology studies:

A. Study title: Phototoxicity tests in rabbits.

Key study findings:

- Adequacy of the study is questionable as inadequate control groups
- However, 1 out of 4 sites that were irradiated after S-Caine Peel application showed well-defined/moderately severe erythema and slight-moderate edema

Study no.: 0432LZ03.001
Volume #, and page #: 14, 14-190
Conducting laboratory and location: [redacted]
Date of study initiation: 24 October 2003
GLP compliance/QA reports: yes (X) no ( )
Drug, lot #, and % purity: S-Caine™ Peel/PE01806/, ~ % for lidocaine and tetracaine
Formulation/vehicle: NA; positive control of 0.5% 8-MOPS
Doses: 0.2 mL on 4 cm^2 site
Study design: Rabbits (N=3/sex/group) were used. Group 1 was treated with mineral oil, positive control, or S-Caine™ Peel for 15 mins, then the skin was irradiated at to non-erythemogenic (i.e, uV greater than 280 nm or ~163 joules,cm^2) at a distance of 10 inches for 60 mins. After the irradiation, the peel was removed and Draize scoring was performed. Group 2 was irradiated for 60 mins as outlined above, the mineral oil, positive control, or S-Caine™ Peel was applied and allowed to dry for 15 mins. All treatments remained in place for 60 mins, after which they were removed and Draize scoring was performed. An untreated site was also included on each animal. Draize scoring was performed at 24, 48, 72, and 96 hrs after treatment completion.

Results:
One out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. No other affects were observed. The adequacy of the study is questionable as there are study design confounds which include: 1) the absorption spectrum of the product is unknown; 2) the correct control groups were not included; and 3) it is unknown if the stratum corneum is affected by removal of the peel. The absorption spectrum information is important because I can not confirm that the wavelength used in the study (erythemogenic - uV greater than 280 nm or ~163 joules,cm^2) is the wavelength that should have been used in the study. The wavelength to use in these studies depends on what wavelengths are absorbed by the drug. If the drug product does not absorb between 290 and 700 nm then phototoxicity is not likely to be a safety concern, but without the information on the absorption spectrum the interpretation of the study results is that S-Caine™ Peel treatment may cause irritation at the site of application if exposed to sunlight.

Dermal Observations/Post Treatment

	24 Hours															
Rabbit	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2*	2*	0	0	3	2	0	0	1*	0	0	0	0	0	0	0
1329♂	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0
1331♀	1*	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
mean	0.5	0.3	0.0	0.0	2.7	2.8	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.8	0.0	0.0	0.5	0.4	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0

	48 Hours															
Rabbit	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2*	1*	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1331♀	1*	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
mean	0.5	0.2	0.0	0.0	2.8	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.4	0.0	0.0	0.4	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

ER = erythema
ED = edema
♂ = Male
♀ = Female
Sites 1 & 2 = Test article
Sites 3 & 4 = Vehicle
Sites 5 & 6 = Positive control (8-MOP)
Sites 7 & 8 =Untreated
Sites 1, 3, 5 and 7 (left side) irradiated after treatment
Sites 2, 4, 6 and 8 (right side) irradiated prior to treatment

*This score is attributed to mechanical damage occurring during test material removal after treatment and light exposure. Difficulty was experienced in test article removal in all six animals after treatment (test article/light exposure).

Dermal Observations/Post Treatment

Rabbit	72 Hours															
	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2A*	0	0	0	3	1	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1331♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
Mean	0.3	0.0	0	0	3.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rabbit	96 Hours															
	Site 1		Site 3		Site 5		Site 7		Site 2		Site 4		Site 6		Site 8	
No.	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
1328♂	2A*	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
1329♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1330♂	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1331♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
1332♀	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0	0
1333♀	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0
Mean	0.3	0.0	0.0	0.0	2.8	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.8	0.0	0.0	0.0	0.4	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

ER = erythema
ED = edema
A = 1/3 of area of test area
♂ = Male
♀ = Female

Sites 1 & 2 = Test article
Sites 3 & 4 = Vehicle
Sites 5 & 6 = Positive control (8-MOP)
Sites 7 & 8 =Untreated

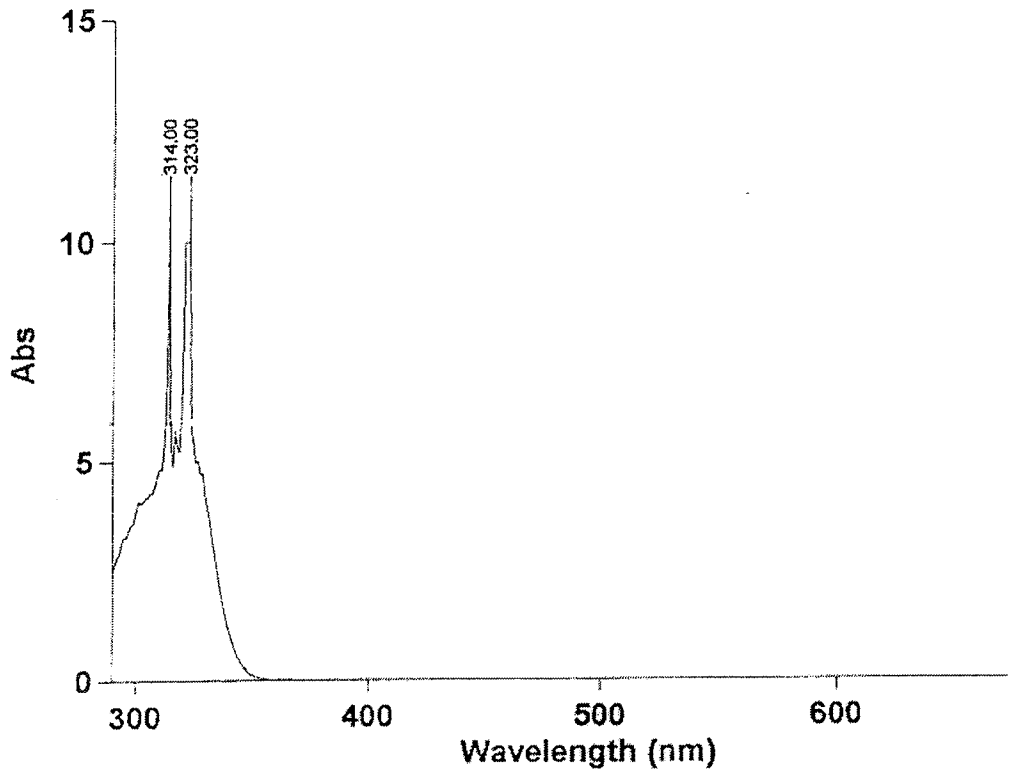
Sites 1, 3, 5 and 7 (left side) irradiated after treatment
Sites 2, 4, 6 and 8 (right side) irradiated prior to treatment

*This score is attributed to mechanical damage occurring during test material removal after treatment and light exposure. Difficulty was experienced in test article removal in all six animals after treatment (test article/light exposure).

The control groups used in the study are inadequate. The Sponsor conducted the study with an untreated control and an ethanol control. No placebo peel was included, therefore, it is difficult to determine if the one reaction was a result of the active ingredients or the peel components themselves. A more adequately designed study should have included sites that were treated with drug only (no light), vehicle (with and without light) or light only. The group in the study that was irradiated and then had the S-Caine™ Peel applied is an inadequate control because if the drug has any anti-inflammatory effect it might mask the erythema and edema even when applied after the light.

Information regarding the absorption spectrum, affect of peel removal on the stratum corneum, and phototoxicity on the placebo peel were requested from the Sponsor.

The absorption spectrum received from the Sponsor (below) indicates that the peel absorbs light ~312-314 nm range.



The Sponsor indicated that no phototoxicity was conducted with the S-Caine™ Peel placebo. In this light, it is difficult to determine if the reaction was a result of components in the peel or a result of the active components.

The affect of the peel on the stratum corneum is unknown, but according to the Sponsor there is no evidence that layers of the epithelium are removed when then peel is removed.

2.6.6.9 Discussion and Conclusions:

The sponsor conducted a standard fertility and reproductive toxicity and a pre- and postnatal development study in rats with tetracaine base at doses up to 7.5 mg/kg. Clinical observations in both studies were decreased activity, prostration, rapid breathing, and scabs at the injection site at a dose of 7.5 mg/kg. In the pre- and postnatal development study, 3 dams (2 dams at a dose of 2.5 mg/kg, 1 dam at a dose of 7.5 mg/kg) were found dead during gestation. The cause of death in these three animals is not known, however, due to the lack of a clear dose-relationship, these deaths do not appear to be attributable to the tetracaine. Body weight gains were decreased in the fertility study in male rats at a dose of 7.5 mg/kg during the entire treatment period, decreased in female rats in all treated groups during premating, and

at a dose of 7.5 mg/kg during GD 0-7. Body weight gains were also decreased in the pre- and postnatal development study during gestation at a dose of 7.5 mg/kg and in all treated groups during LD 0-4. There were no affects of tetracaine base on male or female fertility or pre- and postnatal development.

S-Caine™ Peel (7% lidocaine, 7% tetracaine) was found to produce mild irritation in rabbits, but did not cause any irritation in neonatal piglets. In all animal species examined lidocaine > tetracaine for exposure and there was a delay in T_{max} due to a re-distribution from the skin to the systemic exposure after peel removal.

Experimental shortcomings in the phototoxicity study make it difficult to interpret, but 1 out of 4 sites that were irradiated after peel application showed well-defined/moderately severe erythema and slight-moderate edema. The results of the test indicate a possibility of a phototoxic reaction if treated skin is exposed to sun light as the absorption spectrum indicates S-Caine™ Peel absorbs light in the 312-314 nm range.

2.6.6.10 Tables and Figures: Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY: Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Unresolved toxicology issues: There are two unresolved issues which are discussed below:

1) In light of the problems with the current phototoxicity study regarding the lack of appropriate controls, the unknown affect of the peel on the stratum corneum, and the observation that human subjects in the clinical trials that lidocaine may be present in the body for up to 24 hrs (no data are available for tetracaine as it was not detected) there is a safety concern regarding the possible photo-irritation at the application site. It is unclear if the stratum corneum is removed when the peel is removed, although the Sponsor indicates that there is no evidence from the clinical trials that it is removed. It should be noted that a specific study was not conducted to address the removal of the stratum corneum when the peel is removed. In this light, if the stratum corneum is removed, either partially or completely, then it is probable that the skin with be sensitive to sun, not as a result of the drug's light absorption or photochemical properties, but as a result of physical disruption of the skin's integrity. This concern regarding photo-irritation can be adequately addressed in product labeling and will not require any further non-clinical testing.

2) Eye irritation was not assessed in non-clinical or clinical trials. While there is no indication that the components or active ingredients, lidocaine and tetracaine, of the S-Caine™ Peel cause eye irritation, the potential of the active ingredients, lidocaine and tetracaine, to anesthetize the eyelid is highly likely if they are contacted by the S-Caine™ Peel. This concern regarding eye toxicity can be adequately addressed in product labeling and will not require any further non-clinical testing. The Sponsor has in their proposed label.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

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9/3/04 12:51:25 PM
PHARMACOLOGIST

R. Daniel Mellon
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PHARMACOLOGIST
I concur

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

ADDENDUM TO PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-717**
SERIAL NUMBER:	**N000**
DATE RECEIVED BY CENTER:	**11/17/2003**
DRUG NAME:	**7% lidocaine/7% tetracaine (S-Caine™ peel)**
INDICATION:	**local dermal anesthesia on intact skin**
SPONSOR:	**Zars, Inc.**
DOCUMENTS REVIEWED:	**18 of 102 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Pratibha Rana**

Date of review submission to Division File System (DFS): 10 September 2004

EXECUTIVE SUMMARY

Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective with a Phase commitment.

B. Recommendation for nonclinical studies.
As previously conveyed to the Sponsor for NDA 21-623 (S-Caine™ Patch), the affect of lidocaine on male fertility has not adequately been addressed. A non-clinical study characterizing the effects of lidocaine on male fertility and early embryonic development will need to be conducted. An appropriate study design will include male rats being treated daily for at least 4 weeks prior to mating, 2 weeks of mating, and through gestation, until euthanasia. You should provide data that characterizes the effects of lidocaine treatment each of the following endpoints: 1) maturation of gametes; 2) mating behavior; 3) fertility; 4) sperm counts in epididymides or testes; 5) sperm viability, motility and morphology; 6) histopathology of male reproductive organs (epididymis, testis, seminiferous tubules); and 7) standard female reproductive data parameters.

The sponsor was informed that a male fertility and early embryonic development study for lidocaine was required for approval of the NDA 21-623 (the S-Caine Patch). I reviewed a protocol for the study and found the basic design adequate. The Division received an unaudited draft of the study report on 08 September 2004; however, formal review of the study results can not be completed prior to the planned action date of September 15, 2004. As this study has been completed and the final study report is close to finalization, and since there is low systemic absorption and exposure of lidocaine following dermal application, the male fertility study can be conducted as a Phase 4 commitment. Appropriate wording regarding the lack of information on male fertility will be added to the label until completion of the commitment.

Additional Recommendations on labeling.

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via

[redacted]

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

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

/s/

Suzanne Thornton-Jones
9/10/04 12:25:16 PM
PHARMACOLOGIST

R. Daniel Mellon
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I concur