I. GENERAL INFORMATION

A. File Number

NADA 141-047

B. Sponsor

Fort Dodge Laboratories
800 5th Street N.W.
Fort Dodge, IA 50501-0518

C. Proprietary Name

Torbugesic-SA (butorphanol) Veterinary Injection

D. Established Name

butorphanol

E. Dosage

The recommended dosage in cats is 0.4 mg of butorphanol. per kilogram body weight (0.2 mg/lb) given by subcutaneous injection. This is equivalent to 1.0 mL of Torbugesic-SA (2 mg/mL) per 10 lbs body weight. Pre-clinical model studies and clinical field trials in cats demonstrated that the analgesic effects of butorphanol persist in the majority of responding cats for approximately 3 to 6 hours following subcutaneous injection. In the clinical field trials. the average onset of action was approximately 20 minutes following subcutaneous injection. The butorphanol dosage may be repeated up to 4 times per day for up to 2 days.

F. Dispensing Status

Prescription

G. Species/Class

cats

H. Indication

TORBUGESIC-SA (butorphanol tartrate, USP) is indicated for the relief of pain in cats caused by major or minor trauma. or pain associated with surgical procedures.

II. EFFECTIVENESS

A. Dose - Response Study In Cats

1. Title: Subcutaneous Dose-Response of Butorphanol for Somatic and Visceral Analgesia in the Cat.

2. Investigator:

   Donald C. Sawyer, DVM, PhD
   Michigan State University
   East Lansing, Michigan 48824

3. General Design of the Investigation The **purpose** of the study was to evaluate the analgesic effects of butorphanol in the cat.

   Test animals included 8 healthy female domestic cats, approved for use in these studies by the Michigan State University All University Committee on Animal Facilities and Care. The cats were trained for the experimental procedures and housed in individual cages in a room without other animals.

   To induce somatic responses, electrodes were secured to either shaved forelimb with self-adhering wrap. For stimulation of visceral receptors, a 12F Foley catheter with a 42 mL balloon incorporated, was inserted approximately 7 cm into the colon. The levels of somatic and visceral stimulation to elicit a minimum response were determined during training sessions for each individual cat. For somatic responses, mild electrical currents in increments of 0.05 milliamps were applied to the electrode until at least 2 of the following were observed; a blink, movement of the leg, or flinch. To ensure that the electrode stimulus was at a low level, it was periodically tested on the investigator's finger. The feeling was described as a tingling sensation. For visceral responses, the balloon in the colon was inflated with air in 3 mL increments until the cat strained as if preparing to defecate, and was usually accompanied by panting or heavy breathing.

   The animals in the study served as their own controls and **control** baseline readings were established in each cat during a 15 to 20 minute control period prior to every experiment during which several subthreshold inflations of the balloon were given, randomly interspersed with threshold inflations in a 5:1 ratio. Since the sights and sounds and movements were the same whether pain was elicited or not, the cat could not learn to anticipate a painful stimulus. If, during the control period, an uncharacteristic amount of air was required to elicit a response, the experiment would not be continued. There was negligible drift in baseline values during the entire experimental period.

   The procedure was **blinded** by virtue of the fact that the person inflating was different from the person observing and recording the response.

   Dosage form of butorphanol used in the study was a 2 mg/mL injectable solution prepared by the investigator by dilution (with sterile saline) of the 10

mg/mL butorphanol preparation supplied. Thus the dosage form used was identical in concentration to that proposed to be marketed.

Dosages and routes of administration of butorphanol were 0.2, 0.4, and 0.8 mg/kg subcutaneously.

Test duration. Ten minutes post injection, the electrode testing began with a low level, 1 second stimulus. If the cat's response was positive, the testing ended for that interval but was then repeated sequentially at 10 minute intervals. If the cat's response was negative, the electrical stimulus was increased by 0.05 milliamps until a positive response was seen or the stimulus reached 0.27 milliamps as the upper limit.

If the response to balloon inflation was positive, the balloon was deflated and the testing was terminated for that interval. If there was a negative response, the balloon was deflated and reinflated with an additional 3 mL of air. This procedure was repeated until a positive response was observed or until a maximum of 42 mL of air was injected into the balloon.

Other **pertinent parameters measured** were heart rate and respiratory rate determined before drug administration and at the time of mean duration of effect post treatment.

4. Results Visceral Pain-

Average duration of analgesia as well as pre and post treatment heart rates and respiratory rates in cats treated with various dosages of butorphanol subcutaneously are listed in the following table.

Drug/Route	Dosage mg/kg	Duration of Analgesia Min + Sem	Heart Rate Pre Rx	Heart Rate Post Rx	Respiratory Rate Pre Rx	Respiratory Rate Post Rx
Butorphanol/SQ	0.20	159 + 56	173	167	50	57
	0.40	298 + 45	149	162	55	53
	0.80	346 + 13	164	173	60	55

Subcutaneous injection of butorphanol in cats resulted in dosage dependent analgesic effects. In the visceral pain model subcutaneous dosages of 0.4 0.8 mg/kg were required to achieve analgesia as illustrated in the following figure:

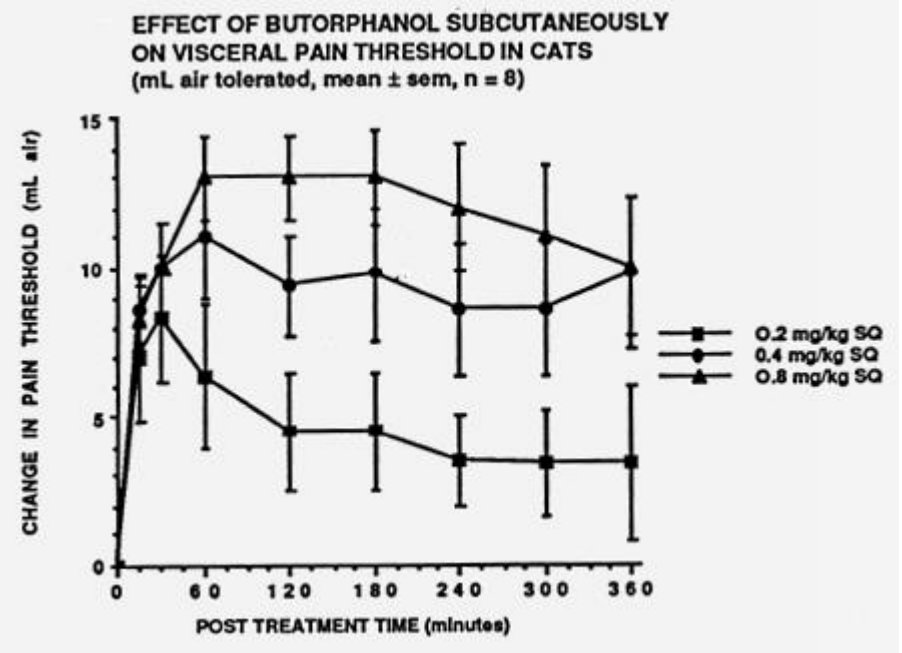
Somatic Pain-

Increased threshold responses were not produced by butorphanol at any doses tested in this somatic pain model.

5. Statistical Analysis For purposes of describing the dose response relationships for butorphanol in the visceral pain model the data were expressed as average change across time (MEAN RESPONSE), duration of measurable change (DURATION), and area under the curve (duration X response). Each of these

parameters was subjected to ANOVA with dosage as grouping variables, at the 0.05 level of significance. The results, showing that subcutaneous dosage of 0.4 mg butorphanol/kg body weight shows analgesia in cats that is indistinguishable statistically from that produced by 0.8 mg/kg is summarized in the following tables.

SUBCUTANEOUS DOSE-RESPONSE SUMMARY STATISTICS (ANOVA)



Parameter	**Dosage**	**n**	**Mean***
Mean Response (delta mL air)	SQ 0.2 mg/kg	8	5.1(a)
	SQ 0.4 mg/kg	8	9.4(b)
	SQ 0.8 mg/kg	8	11.3(b)
Duration (mean, minutes)	SQ 0.2 mg/kg	8	191.3(a)
	SQ 0.4 mg/kg	8	300.0(a,b)
	SQ 0.8 mg/kg	8	345.0(b)
Area Under Curve (Duration X Response)	SQ 0.2 mg/kg	8	1633.1(a)
	SQ 0.4 mg/kg	8	3304.7(b)
	SQ 0.8 mg/kg	8	4184.1(b)

*Means that share a common superscript are not significantly different (p<O.05)

6. Conclusions The results of this study indicate that an analgesic effect of butorphanol for visceral pain in the cat is obtained by subcutaneous injection of 0.4 mg/kg. The drug had no effect on somatic pain in this study.

7. Adverse reactions No discomfort was observed following butorphanol injection, but mydriasis was noted at all doses.

B. Dose Confirmation Study

1. Title: Butorphanol Dose Confirmation Study in Cats.

2. Investigator:

   Marc R. Raffe, DVM, MS
   Professor of Comparative Anesthesiology
   College of Veterinary Medicine
   University of Minnesota
   St. Paul, MN.

3. General Design of the Investigation A dose confirmation study was conducted to confirm the results of the dose determination study which indicated that 0.4 mg/kg was an effective dose of butorphanol in the cat.

   In this experimental study, 12 cats were given 0 (placebo) and 0.4 mg butorphanol per kg body weight by subcutaneous injection. The study was conducted using a cross-over design in which drug treatments were randomly assigned, balanced among treatment, gender and sequence. The study was conducted on a double blind basis in that the investigator and observer were unaware of the drug or dosage given. The randomized sequence of treatment was repeated after a 14 day washout period by crossing over and administering the drug treatment or placebo treatment.

   The **purpose** of the study was to determine the analgesic activity of butorphanol given subcutaneously at the dosage of 0.4 mg/kg in cats, using a somatic pain model.

   Test animals were 12 healthy domestic cats (6 males and 6 females) ranging in age from 8 to 13 months and weighing between 2.27 and 4.24 kg, each of which had a periosteal electrode surgically implanted on the wing of the ileum; the electrodes were connected to a variable voltage generator. To induce pain responses, five second challenges of increasing voltage were applied to the electrodes at 15 second intervals until avoidance behavior, usually a slight movement or twitch, was noted. The voltage, amperage, and time (in seconds) required to elicit the response were recorded as measures of pain threshold.

   Each experiment consisted of four baseline measurements of pain threshold at 15 minute intervals prior to injection of test material at the designated dosage. Following injection, measurements of pain threshold were made at 15 minute intervals for a total of 360 minutes.

Control treatment consisted of a placebo injection followed by evaluation of pain threshold as above.

Diagnosis of pain was based on overt avoidance behavior, usually a slight movement or twitch, that occurred when threshold voltage was reached.

Dosage form was an injectable solution of butorphanol at a concentration of 2 mg/mL, identical to that to be marketed. Placebo injection consisted of vehicle only, without active drug.

Dosages, routes of administration and duration were 0 (placebo control) or 0.4 mg/kg subcutaneously followed by observation periods of six hours.

Pertinent parameters measured at each observation time (every 15 minutes) included the following:

- volts required to elicit a response
- amperage required to elicit a response
- time required to elicit the response
- heart rate (recorded every 30 minutes)
- respiratory rate
- mental awareness (subjective assessment on a scale of -2 = very depressed, to +2 = very agitated)

4. Results Butorphanol at a dosage of 0.4 mg/kg body weight had the effect of increasing pain threshold (both volts and amperage) required to elicit a response to the electrode simulation. The effect of butorphanol on the pain threshold using the somatic pain model is illustrated in the following figures.Threshold voltages post-treatment were significantly higher for butorphanol treated cats as compared to placebo at 30 minutes and from 90 minutes through 135 minutes by the univariate ANCOVA ($P<0.05$, two-sided test). The repeated measures ANCOVAs also found a statistically significant effect of treatment (higher voltages for butorphanol) in the first and second one-hour periods. Using one sided tests, results are also significant ($P<0.05$) at 15 minutes, 45 minutes, 75 minutes, 150 minutes, and 315 minutes.

   Amperages post-treatment were significantly ($P<0.05$) higher for butorphanol as compared to placebo at 30 minutes through 60 minutes and from 90 minutes through 150 minutes using the univariate ANCOVA test. Amperages were also found to be significantly higher in the first three one-hour periods by the repeated measures ANCOVA analysis. Using one-sided tests, results are also significant ($P<0.05$) at 15 minutes, 75 minutes, 210 minutes, 240 minutes, and 270 minutes.

   Although there were some additional statistically significant findings for the other parameters in this study (mental awareness score, reaction time, heart rate, respiratory rate), these occurred much less often (i.e., sporadically), were observed later in the study (relative to treatment administration), and are not believed to be related to butorphanol.

5. Statistical analysis The study data were analyzed using a univariate and repeated analysis of covariance (ANCOVA) for cross-over designs; the terms included in the model were replicate, sex, treatment, period, sequence, cat (within replicate, sex and sequence combination), time, all interactions of the former terms with time, and the baseline taken just prior to treatment as a covariate. Because the plots of mean values indicated differences between treatments in early time points (one to three hours posttreatment), and because of the biological plausibility that efficacy would be most apparent shortly after drug administration, the analysis was segmented into repeated measures ANCOVA for each one hour period (two hours for heart rate). Although this approach has the disadvantage of slightly increasing the overall false-positive rate. it allows one to detect treatment differences that would be diluted (at later times after drug administration, when blood levels of butorphanol decline) by a single overall ANCOVA.

   Significant treatment effects were denoted by a (conservative two sided test) P value less than 0.05. Plots of the pertinent parameters as functions of time and drug dose were also constructed.

Figure 1

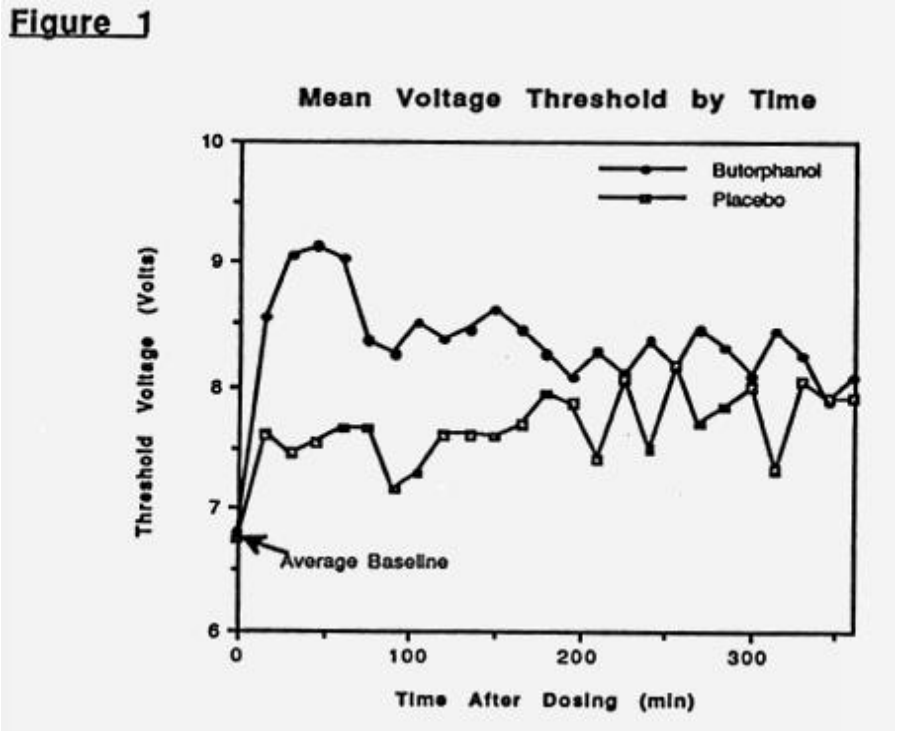
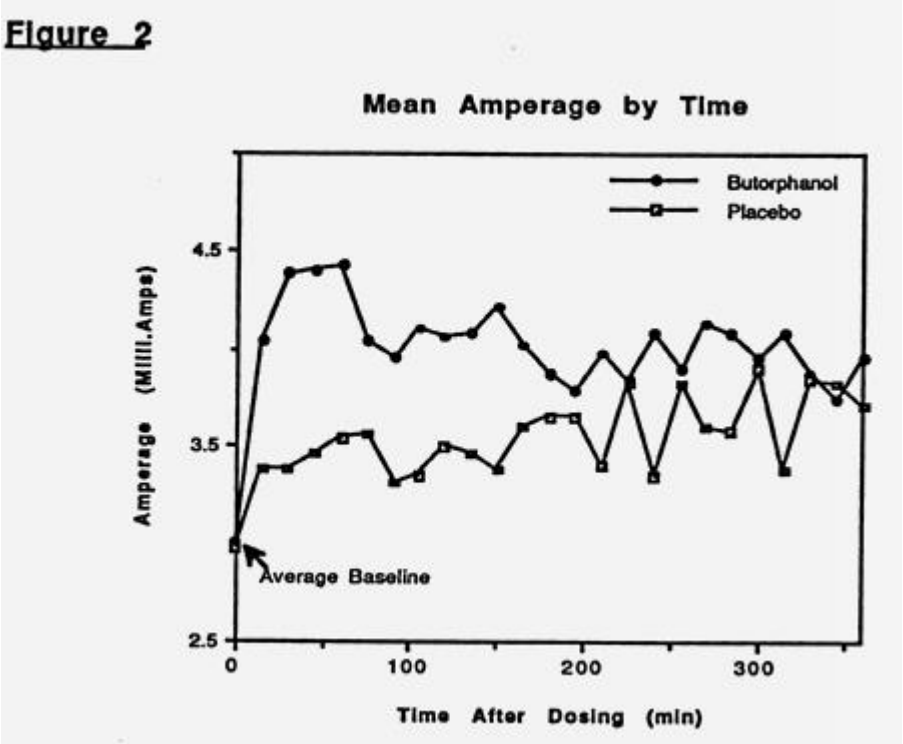


Figure 2



6. Conclusions drawn from the study The results of this study indicate that a butorphanol dosage of 0.4 mg/kg given subcutaneously in cats is effective in producing analgesia to somatic pain. The statistical results (Univariate and repeated measures analyses) indicate that butorphanol significantly ($P<0.05$, two sided test) increases the threshold Voltage at several time points significantly so in the first one hour after injection and marginally ($P=0.0575$) in the second hour. Amperages were significantly increased at an even greater number of points, with significant ($P<0.05$, two sided test) effects seen in the first two hours post-treatment and marginally ($P=0.0734$)in the third hour.

7. The only adverse reaction-reported was pain on injection. The following table shows the incidence of pain with injection of vehicle placebo and butorphanol.

Treatment	**No. of Cats Eliciting Pain**	**No. of Cats without Pain**
Vehicle Placebo	11	1
Butorphanol	6	6

8. Four cats developed lead wire infections during the study which required treatment with antibiotics (amoxicillin or amoxicillin/clavulanate).

C. Controlled Field Investigations of Butorphanol In Cats

1. Title: Clinical Evaluation of Butorphanol Tartrate as an Analgesic in Cats (Blinded Study)

2. Investigators:

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3. General Design of the Investigation The **purpose** of the study was to evaluate the effectiveness and side effect profile of butorphanol given at a dosage of 0.4 mg/kg (0.2 mg/lb) by subcutaneous injection for alleviating pain in cats, under conditions of veterinary practice.

Test animals were cats of any age, weight, or breed which were diagnosed by the veterinarian as experiencing pain. The pain could be the result of major or minor trauma, or originate from painful surgical procedures such as declaws and castrations.

The study was **controlled** by use of a placebo (sterile buffered saline) injection to provide a negative control group of cats with pain similar to the population receiving the active drug, butorphanol. The study was **blinded** by providing the

investigators with coded vials containing either butorphanol or a placebo solution.

The **diagnosis** of pain in the cats was of necessity based on the behavioral changes observed in the animals by the investigators. These behavioral changes may be manifest by aggressive behavior or by withdrawal or depression, and may be expressed by obscure signs such as loss of appetite and unwillingness to urinate or by more obvious signs such as biting, licking or scratching at a painful lesion, lameness, or aggressive behavior when an injured area is manipulated. Accordingly, the pain intensity was standardized by use of a scoring system on a 0 - 4 (normal to severe) basis on individual signs of pain including vocalizing, panting, aggression, withdrawal, and response to manipulation. Additionally, an overall severity of pain score was given to each patient. Finally, the investigators were asked to describe in words any other signs that were consistent with pain.

The **dosage form** of butorphanol was a 2 mg/mL solution in 10 mL vials, identical to the dosage form to be marketed. The control placebo solution was provided in identical vials. The **dosage** of butorphanol was the proposed recommended dosage of 0.2 mg/lb body weight given by the proposed **route of administration**, subcutaneous injection. Thus all cats were given 0.1 mL of active drug or placebo per pound of body weight. The protocol allowed for the dosage to be repeated as needed but no sooner than six hours after the previous dosage and for not longer than seven days (the labeling indicates that butorphanol can be safety repeated up to 4 times per day for up to 2 days because the subacute safety study was conducted at 4 times per day for 6 days which is 3 times the duration of use).

Pertinent parameters measured included the clinical signs of pain as well as the clinical scores as described above, before treatment and after treatment. Heart rate was also determined before and after treatment. The investigators were also asked to state how soon after treatment they felt analgesia had become evident and what the duration of analgesic activity was. Finally, investigators were asked to report on each case whether or not they observed an analgesic effect (yes or no) and to give an overall evaluation on the following basis:

EXCELLENT Injection produced a marked analgesic effect making the subject comfortable and relaxed, improved subject's attitude, and promoted a smoother convalescence.

GOOD Injection produced a noticeable analgesic effect, making the subject somewhat more comfortable and relaxed.

FAIR Injection produced only a slight analgesic effect.

POOR No noticeable analgesic effect.

4. Results Case reports on a total of 64 cats were received of which 33 were treated with butorphanol and 31 with placebo (see Appendix I, pages 30-31 for a description of each butorphanol-treated case). The following table shows

the clinical conditions which necessitated analgesic therapy and the number of cases treated with butorphanol and placebo for each condition:

	BUTORPHANOL (n=31)	**PLACEBO (n=33)**
Declaw	13	10
Abscess/cellulitis	6	7
Musculoskeletal	4	8
Neuter/Spay	2	4
Trauma	2	2
Soft Tissue Injury	2	0
Miscellaneous	2	2

Clinical pain scores before and after treatment for all enrolled cases are summarized in the following table [the values below represent the mean scores (0-4) from those cats showing that particular pain parameter, i.e., not every cat showed aggression during the study]:

SUMMARY OF CLINICAL PAIN SCORES IN CATS

	Mean pain score (0-4) for parameter indicated			
	PLACEBO		**Respiratory Rate**	
Pain Parameter	**Pre Rx**	**Post Rx**	**Pre Rx**	**Post Rx**
Vocalizing	1.5	1.2	1.5	0.9
Panting	0.3	0.3	0.2	0.0
Aggression	1.6	1.3	1.4	0.7
Withdrawal	2.4	1.8	2.4	1.0
Pain on manipulation	3.3	2.4	3.2	1.7
Total Score*	9.1	7.0	8.7	4.3

*Average of sum of individual pain scores

The mean overall pain score in the placebo group was 2.8 (scale 0-4) prior to treatment and 2.2 after treatment. For butorphanol, the mean overall pain score was 2.7 prior to treatment and 1.5 after treatment.

Signs of pain other than those listed in the table above (ex. non-weight bearing, not eating, reluctant to move) were noted in 18 placebo and 20 butorphanol cats prior to treatment. Improvement in these signs of pain was noted in 5/18 (28%) placebo-treated cats and in 16/20 (80%) butorphanol-treated cats. Other comments noted on the case reports from those cats responding to the drug, although difficult to quantitate, indicated that butorphanol made the subjects more comfortable, shortened the convalescence period, and made management easier, when compared to placebo.

Finally, the overall analgesic effect of the drugs was rated as satisfactory ('excellent' or 'good')in 19/28 (68%) butorphanol-treated cats compared to 7/25 (28%) placebo-treated cats. (Note that these data came from six out of the thirteen investigators who enrolled cases in both treatment groups, see statistical analysis.)

PROPORTION OF CATS EVALUATED AS EXCELLENT OR GOOD

INVESTIGATOR	**BUTORPHANOL**	**PLACEBO**
Bradshaw	4/4	0/1
Bruck	5/5	0/5
Carter	2/5	1/5
Gruss	3/5	3/5
Smith	2/5	1/5
Wood	3/4	2/4

The average duration of the analgesic effect was approximately 4 hours (range 15 minutes to 8 hours), with an average onset of activity of approximately 16 minutes after injection.

5. Statistical analysis Statistical analysis was performed on data from the six investigators (Bradshaw, Bruck, Carter, Gruss, Smith, and Wood) who had cases in both treatment groups (total of 28 cats treated with butorphanol and 25 treated with the placebo) so that a comparison of the control and treated groups could be made for each investigator and across investigators. The data generated by the remaining seven investigators remains in the data base for determination of clinical safety and calculations of the duration and onset of analgesia.

   A procedure for comparing proportions from m independent samples as described by Fleiss (1981) was used to test for investigator effect [Fleiss, J.L. (1981) In: *Statistical Methods for Rates and Proportions.* 2nd ed. John Wiley & Sons, New York. pp 138-143]. This procedure was applied both to the proportion of cats showing an analgesic response (yes or no) as well as proportion of "excellent" or "good" responses (satisfactory) vs. "fair" or "poor" responses (unsatisfactory) between butorphanol and placebo groups. There was no association ($p > 0.05$) between investigator and the evaluation of an analgesic effect (yes or no) or the overall evaluation of the response of the cats to butorphanol (excellent, good, fair, or poor).

   The determination of the statistical significance in analgesia between placebo and butorphanol treated patients was performed using the zstatistic of the difference of two rates as described by Fleiss [Fleiss, J.L. (1981) In: *Statistical Methods for Rates and Proportions.* 2nd ed. John Wiley & Sons, New York. pp 100-111]. The difference in response between butorphanol and placebo was statistically significant ($p<0.05$) with regard to both analgesic effect (yes or no) and proportion of 'excellent" or "good" responses (satisfactory) vs. "fair" or "poor" responses (unsatisfactory).

   Ridit analysis was used to take advantage of the ordered nature of the scoring of analgesic response (excellent>good>fair>poor). The statistical significance

of the difference between the mean ridit values for the two treatments was tested using the z-statistic and found to be highly significant ($p < 0.005$).

6. Conclusions Results of this study confirm clinically and statistically that butorphanol given subcutaneously at a dosage of 0.4 mg/kg is an effective and safe analgesic in the cat, when tested under conditions of veterinary practice.

   Approximately 68% of treated cats can be expected to have a satisfactory analgesic response to the drug.

7. Adverse Reactions The following table shows the adverse effects observed in this study:

CLINICAL SIGN	**BUTORPHANOL**	**PLACEBO**
Pain on Injection	5/33 (15%)	4/31 (13%)
Mydriasis	4/33 (12%)	0/31 (0%)
Disorientation	2/33 (6%)	0/31 (0%)
Sedation	1/33 (3%)	0/31 (0%)

D. Controlled Field Investigations of Butorphanol In Cats This study was an extension of the study described above, differing only in the concentration of butorphanol (4 mg/mL as opposed to 2 mg/mL previously used)

1. Title: Clinical Evaluation of Butorphanol Tartrate as an Analgesic in Cats (Blinded Study)

2. Investigators:

Randall Bradshaw, DVM
Waterlick Plaza
Lynchburg, VA 24502

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Earlysville, VA 22936

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Marcellus, NY 13108

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Wayne Carter, DVM
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Robert F. Malsby, Jr., DVM
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Marietta, GA 30060

Richard T. Goldston, DVM
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3295 62nd Ave N
St. Petersburg, FL 33702

3. General Design of the Investigation The **purpose** of the study was to evaluate the effectiveness and side effect profile of butorphanol given at a dosage of 0.4 mg/kg (0.2 mg/lb) by subcutaneous injection for alleviating pain in cats, under conditions of veterinary practice.

   Test animals were cats of any age, weight, or breed which were diagnosed by the veterinarian as experiencing pain. The pain could be the result of major or minor trauma, or originate from painful surgical procedures such as declaws and castrations.

   The study was **controlled** by use of a placebo (sterile buffered saline) injection to provide a negative control group of cats with pain similar to the population receiving the active drug, butorphanol. The study was **blinded** by providing the investigators with coded vials containing either butorphanol or a placebo solution.

   The **diagnosis** of pain in the cats was of necessity based on the behavioral changes observed in the animals by the investigators. These behavioral changes may be manifest by aggressive behavior or by withdrawal or depression, and may be expressed by obscure signs such as loss of appetite and unwillingness to urinate or by more obvious signs such as biting, licking or scratching at a painful lesion, lameness, or aggressive behavior when an injured area is manipulated. Accordingly the pain intensity was standardized by use of a scoring system on a 0 - 4 (normal to severe) basis on individual signs of pain including vocalizing, panting, aggression. withdrawal, and response to manipulation. Additionally, an overall severity of pain score was given to each patient. Finally, the investigators were asked to describe in words any other signs that were consistent with pain.

   The **dosage form** of butorphanol was a 4 mg/mL solution in 10 mL vials, more concentrated than the 2 mg/mL dosage form to be marketed. Supplies of the more concentrated solution were available and were used in this trial since all other aspects of the formulation were the same as proposed for market. The control placebo solution was provided in identical vials. The **dosage** of butorphanol was the proposed recommended dosage of 0.2 mg/lb body weight given by the proposed **route of administration**, subcutaneous injection. Thus all cats were given 0.05 mL of active drug or placebo per pound of body weight.

   Pertinent parameters measured included the clinical signs of pain as well as the clinical scores as described above, before treatment and after treatment. Heart rate was also determined before and after treatment. The investigators were also asked to state how soon after treatment they felt analgesia had become evident and what the duration of analgesic activity was. Finally, investigators were asked to report on each case whether or not they observed an analgesic effect (yes or no) and to give an overall evaluation on the following basis:

   EXCELLENT Injection produced a marked analgesic effect making the subject comfortable and relaxed, improved subject's attitude, and promoted a smoother convalescence.

GOOD Injection produced a noticeable analgesic effect, making the subject somewhat more comfortable and relaxed.

FAIR Injection produced only a slight analgesic effect.

POOR

No noticeable analgesic effect.

4. Results Case reports on a total of 83 cats were received from the seven investigators of which 40 received butorphanol and 43 received placebo. (see Appendix II, pages 32-33, for a description of each butorphanol treated case). The following table shows the clinical conditions which necessitated analgesic therapy and the number of cases treated with butorphanol and placebo for each condition:

	BUTORPHANOL (n=40)	**PLACEBO (n=43)**
Declaw	22	19
Abscess/cellulitis	2	5
Musculoskeletal	6	7
Neuter/Spay	1	3
Trauma	4	4
Soft Tissue Injury	1	2
Miscellaneous	4	3

Butorphanol injection resulted in decreased vocalization, panting, aggression, withdrawal, pain on manipulation, and overall pain scores. These responses were numerically greater in the butorphanol treated cats than in placebo controls, as summarized in the following table.

BUTORPHANOL DOUBLE BLIND CLINICAL DATA SUMMARY

		NUMBER			**AVERAGE VALUE**		
PARAMETER	**DRUG**	**PRE**	**POST**	**%CHG**	**PRE**	**POST**	**CHANGE**
Vocalization (1-4)	Butorphanol	24	15	37.5	2.4	1.0	1.4
	Placebo	28	26	7.1	2.3	1.9	0.4
Panting (0-4)	Butorphanol	12	5	58.3	1.6	0.6	1.0
	Placebo	14	13	7.1	1.4	1.3	0.1
Aggression (0-4)	Butorphanol	26	11	57.7	2.2	0.7	1.5
	Placebo	21	20	4.8	2.5	2.4	0.1
Withdrawal (0-4)	Butorphanol	39	27	30.8	2.6	1.1	1.5
	Placebo	40	36	10.0	2.5	2.2	0.3
Pain on Manipulation (0-4)	Butorphanol	40	33	17.5	2.9	1.3	1.6
	Placebo	43	38	11.6	3.0	2.5	0.5
Overall Pain (0-4)	Butorphanol	40	34	15.0	2.6	1.3	1.3
	Placebo	43	39	9.3	2.5	2.2	0.3

NUMBER in the above table refers to the number of cats displaying each pain parameter before and after treatment; AVERAGE VALUE refers to the average score of all cats displaying each pain parameter before and after treatment.

Heart rate decreased an average of 19 and 13 beats per minute in the butorphanol and placebo groups, respectively, with wide variation in response between individuals.

In the butorphanol group, 79% of the cats reportedly showed analgesia (yes vs no) compared to 22% in the placebo group. Overall favorable clinical ratings (good or excellent) were given in (29/39) 74% of the butorphanol cases compared with (8/41) 20% of the placebo cases, broken down as shown below. (Note that these data came from five out of the seven investigators who enrolled 10 cases or more. Two of the investigators enrolled only one and two cases, respectively, and were not considered appropriate for inclusion in the statistical analysis. The data from these two investigators were included in the data base for evaluation of clinical safety and determination of the duration and onset of analgesia.)

PROPORTION OF CATS EVALUATED AS EXCELLENT OR GOOD

INVESTIGATOR	**BUTORPHANOL**	**PLACEBO**
Bradshaw	6/7	0/9
Bruck	10/10	0/10
Goldston	4/5	0/5
Gruss	6/10	5/10
Malsby	3/7	3/7

The average duration of the analgesic effect was approximately 4 hours (range 1 to 7 hours), with an average onset of activity of approximately 16 minutes after injection.

5. Statistical analysis Statistical analysis was conducted on data generated by five of the seven investigators who reported on 10 cases or more (see table above). Among these investigators there appeared to be differences in efficiency of detecting analgesic response to butorphanol. The difference between treatment groups with regard to satisfactory response (excellent or good) was tested using Fisher's exact test. The treatment differences (in favor of butorphanol) were significant ($p<0.01$) for investigators Bradshaw, Bruck, and Goldston, but not for Gruss and Malsby.

   The significance of the apparent differences between butorphanol and placebo for the changes (pretreatment - post treatment) for each of the response variables listed in the summary table above was tested by the non-parametric Mann Whitney U test at the nominal 0.05 level of significance. The analgesic responses were significantly ($p< 0.05$) greater in butorphanol-treated cats than in placebo controls with regard to all individual clinical score parameters.

   The significance of the difference between dosage groups with regard to change in heart rate was tested by 2-factor analysis of variance with treatment and investigator as grouping variables. The difference in heart rate reduction between butorphanol and placebo was not significantly different ($p> 0.05$) nor was there significant investigator-treatment interaction.

6. Conclusions Results of this study confirm clinically and statistically that butorphanol given subcutaneously at a dosage of 0.4 mg/kg is an effective and safe analgesic in the cat, when tested under conditions of veterinary practice.

Approximately 74% of treated cats can be expected to have a satisfactory analgesic response to the drug.

7. Adverse Reactions The following table shows the adverse effects observed in this study:

CLINICAL SIGN	**BUTORPHANOL**	**PLACEBO**
Pain on Injection	6/40 (15%)	12/43 (28%)
Mydriasis	2/40 (5%)	0/43 (0%)
Disorientation	1/40 (2.5%)	0/43 (0%)

E. Clinical Evaluation of Butorphanol as an Analgesic in Cats

1. Objectives This was a preliminary, open field investigation, the purpose of which was to determine whether or not butorphanol injection would provide clinically detectable analgesia in the cat, what the clinical signs of pain in cats would be, and whether subcutaneous dosage of 0.1 mg/lb (0.2 mg/kg) would be as effective as 0.2 mg/lb (0.4 mg/kg) under conditions of veterinary practice. These studies were conducted partly to refine the dosage to be recommended for larger scale clinical testing.

2. Investigators:

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Richard T. Goldston, DVM
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3507 U.S. 19St.
Spring Hill, FL 33526

3. General Design of the Investigation: . Cats entering the study could be of any age, weight, sex, or breed that presented with pain, which could be the result of trauma or originate from painful surgical procedures.

   Prior to administration of butorphanol, investigators were asked to list those clinical signs suggestive of pain. After treatment investigators were asked to record their observations that indicated the cat Was in less pain. Investigators then evaluated the analgesic effect as "excellent", "good", "fair", or "poor" as defined in the protocol (refer to pages 13 and 18 of the FOI Summary for definitions). Investigators also noted the number of minutes following injection that analgesia was first noted and the approximate duration of analgesia.

   Test drug was supplied as a 0.5 mg/mL formulation of butorphanol in 10 mL vials. Dosing schedules were provided to each investigator for assignment of either 0.1 or 0.2 mg/lb dosages to each case. Cats were dosed as needed, but no sooner than every 6 hours.

4. Results Case reports on a total of 58 cats were received of which 36 were given 0.1 mg/lb, 21 were given 0.2 mg/lb. One cat was inadvertently given 0.05 mg/lb and was excluded from the study.

   The following table shows the clinical conditions which necessitated analgesic therapy and the number of cases that received each dose of butorphanol with each condition:

	0.1 mg/lb (n=36)	**0.2 mg/lb (n=21)**
Declaw	11	6
Abscess/cellulitis	6	3
Musculoskeletal	9	5
Neuter/Spay	2	2
Trauma	3	2
Soft Tissue Injury	3	1
Miscellaneous	2	2

   The most frequent signs of pain noted by the investigators were vocalizing, withdrawal, aggression, and panting, which subsided following butorphanol treatment at either dosage. Mean heart rate declined after treatment in both treatment groups. The numbers of cats displaying each parameter before and after treatment and the average heart rates before and after treatment are summarized in the following table.

Summary of Study on Butorphanol Analgesia in Cats

	0.1 mg/lb			**0.2 mg/lb**		
	pre Rx	**post Rx**	**percent change**	**pre Rx**	**post Rx**	**percent change**
Vocalizing	23	7	70	16	3	81
Withdrawal	27	5	81	16	4	81
Aggression	9	3	66	10	1	75
Panting	5	0	100	5	1	80
Heart Rate (mean)	162	153	5.5	190	182	4.2

The onset of analgesia was similar in both dosage groups, averaging approximately 17 minutes in the 0.1 mg/lb group and 24 minutes in the 0.2 mg/lb group. The duration of analgesia was approximately 5 hours (range 3 to 8 hours) in the 0.1 mg/lb group and 4 hours (range 1.5 to 6.5 hours) in the 0.2 mg/lb group. The following observations which the investigators felt were indicative of pain relief in the cats following butorphanol treatment were noted:

OBSERVATION	**0.1 mg/lb**	**0.2 mg/lb**
More comfortable	31/36 (86%)	20/21 (95%)
Smoother convalescence	27/36 (75%)	18/21 (86%)
Shorter recovery period	14/36 (39%)	9/21 (43%)
Management easier	27/36 (75%)	16/21 (76%)
Faster return to normal attitude	23/36 (63%)	17/21 (81%)

The investigators rated the overall analgesic effect as 'excellent' or "good" in 78% (28/36) of the cats given butorphanol at 0.1 mg/lb, and in 95% (20/21) of the cats in the 0.2 mg/lb dosage group.

Due to the limited number of cases and the paucity of numerical criteria for evaluation, statistical analysis was not performed.

Adverse effects noted consisted of pain on injection, dilation of pupils (mydriasis), disorientation, sedation, and swallowing and licking (see following table):

CLINICAL SIGN	**0.10 mg/lb**	**0.20 mg/lb**
Pain on Injection	6/36 (17%)	1/21 (5%)
Mydriasis	6/36 (17%)	2/21 (10%)
Disorientation	3/36 (8%)	2/21 (10%)
Sedation	1/36 (8%)	0/21
Swallowing/Licking	1/36 (3%)	1/21 (5%)

5. Conclusions Results of this study indicated that: 1) butorphanol is an effective analgesic in the cat, 2) analgesia can be detected by careful observation of behavioral signs, and 3) that the 0.2 mg/lb subcutaneous dosage gives a satisfactory analgesic response which is more dependable than the lower dosage tested. On the basis of these study results it was decided that in future

studies the list of signs of pain should be expanded, that each sign should be given a numerical score in order to provide data for statistical analysis, and that 0.2 mg/lb (0.4 mg/kg) is the preferred clinical dosage.

III. TARGET ANIMAL SAFETY

A. A. Subacute Toxicity Study of Butorphanol in Cats

1. Title: Twenty-One Day Subcutaneous Safety Evaluation of Butorphanol in Cats

2. Investigator:

   J.A. Botta, Jr., DVM, PhD
   T.P.S. Inc.
   10424 Middle Mt. Vernon Road
   Mt. Vernon, IN 47620

3. General Design of the Investigation The **purpose** of the study was to evaluate the effects of butorphanol injected subcutaneously to cats at levels of 1, 3, or 5 times the anticipated clinical dosage of 0.4 mg/kg.

   Test animals were 24 young adult domestic shorthair cats of random source, of both sexes (8 males, 16 females), weighing 1.7 to 4.5 kg at initiation. The cats were individually housed in metal cages in an >environmentally controlled facility, and provided with Purina cat chow and fresh water *ad libitum.* The cats were randomly sorted by a computer generated (RANAN) randomization program into 4 dosage groups of 6 cats per group, each group represented by 2 males and 4 females.

   The dosage form used was an injectable formulation containing 2 mg butorphanol per mL, identical to the formulation to be marketed, supplied in glass vials containing 10 mL. The **control** substance was sterile saline for injection, USP.

   Dosages, routes, and test duration were 0 (saline placebo given in a volume equal to the highest dosage of butorphanol), 0.4, 1.2, and 2.0 mg butorphanol per kg body weight, given by subcutaneous injection 4 times daily during the first 6 days of the investigation (which is 3 times the recommended duration of use of 2 days), then once daily for 15 additional days, for a total of 21 days of dosing. These dosages represent O, 1, 3, and 5 times the anticipated clinical subcutaneous dosage of 0.4 mg/kg.

   Pertinent parameters measured included clinical observations twice daily and during the first hour after dosing, monitoring of body weights and food consumption, physical examination including ophthalmic examination weekly, and complete blood counts and serum chemistry profiles conducted before the experiment and weekly, thereafter. Cats were euthanized and necropsied 24 - 36 hours after the last injection, for complete gross necropsy, determination of organ weights, and histopathology on major tissues and organ systems.

4. Results Clinically, the only sign of drug induced toxicity was a reaction to the repeated injections by the cats as if they caused a burning or stinging sensation for a few seconds after each injection. Signs of respiratory infections (congestion and Conjunctivitis) occurred during the experimental period in controls as well as treated groups (3 cats in the control group, 4 in the 1X group, 2 in the 3X group and 2 in the 5X group). Likewise, body weight fluctuated in all treatment groups, but drug or dosage related trends were not detected, as shown in the following table:

Group	**MEAN BODY WEIGHT (grams)**			
	Week 0	**Week 1**	**Week 2**	**Week 3**
0	2504	2559	2602	2563
1X	2212	2166	2349	2325
3X	2270	2309	2420	2308
5X	2446	2292	2350	2295

Hematology and clinical chemistry results did not reveal any consistent or distinct effects associated with butorphanol treatment. At the end of week 1, the red blood cell count (6.11 X 106), hematocrit (29.2%) and hemoglobin concentration (8 g/dl) were significantly lower in the high dose females compared to the controls (8.05 X 10(6), 36.3% and 10.4 g/dl, respectively). Similar changes were not seen in the male cats or in the high dose females for the remainder of the study. A decrease in the mean total protein value was seen in the mid dose females at week 1 compared to the controls (7.2 g/dl compared to 8.6 g/dl).

At necropsy, there were no apparent treatment or dosage related gross tissue changes other than lesions typical of those expected in random source cats, including roundworms, tapeworms, and ocular and nasal discharge. On Histopathology, focal renal tubular dilation was noted in the high dosage group in one of two males and two of four females but not in other dosage or control groups. Histopathologic changes indicative of minimal to slight irritation were noted at the injection sites in 3 of 6 cats in the low dose group, 4 of 6 cats in the middle dose group and 6 of 6 cats in the high dose group.

5. Conclusions It was thus demonstrated that an ample margin of safety is associated with butorphanol when used as directed at a dosage of 0.4 mg/kg subcutaneously in cats. The results of this study indicate that the only adverse clinical effect of subcutaneously administered butorphanol in cats at a dose of 0.4 mg/kg was pain with injection. Histopathologic changes indicative of minimal to slight irritation at the injection sites are seen at the 1X, 3X and 5X dosages, while focal renal tubule dilation is evident at 5 times the recommended dose.

B. Range Finding Safety Study of Butorphanol in Cats

Four young adult domestic shorthair cats, two males and two females. weighing between 2.1 and 2.9 kg at initiation, were given daily subcutaneous injections of butorphanol at a dosage of 2 mg/kg for one week, 4 mg/kg the following week, 8 mg/kg the following week, and 16 mg/kg the final week. A 2 mg/mL solution of butorphanol, identical to that to be marketed, was used for the 2 and 4 mg dosages, and a 10 mg/mL formulation was used for the 8 and 16 mg/kg dosages due to volume considerations. The cats were observed twice daily, during the first and last hour of the workday, and during the first hour after dosing each day for any signs of toxicity throughout the 28 day dosage period. Physical examinations were conducted pretest and. prior to necropsy. Blood samples were collected before treatment and weekly thereafter for evaluation of hematology parameters. Body weights were recorded pretest and weekly during the study. At the end of the dosing period complete serum chemistry determinations and gross postmortem examinations were conducted on all the cats. Group mean body weights were slightly depressed following four weeks of butorphanol treatment (see table below). This finding could be attributable to the drug or to the stress of frequent clinical procedures. Without a concurrent control group, no definitive conclusions could be made.

	MEAN BODY WEIGHT (kg)
Week 0	2.6
Week 1	2.4
Week 2	2.4
Week 3	2.4
Week 4	2.3

The only clinical signs of toxicity noted during the first three weeks of the experiment were signs of pain ,and resentment of the daily subcutaneous injections in all cats. When dosages were increased to 16 mg/kg during the final week of the experiment, however, all of the cats responded by displaying incoordination, salivation, or mild convulsions. most evident during the first hour after injection. All cats survived the study. At the time of the terminal physical examination, one cat walked with a crab-like side motion. This observation was believed to be due to tenderness in the flank area from the test material injections.

Neither hematology nor serum chemistry evaluations revealed changes suggestive of any drug toxicity. The only changes noted in the hematology data were elevations of the mean corpuscular volume (MCV) at week 1 compared to week 0 (48.3 fl compared to 45 fl) and a decrease in the MCV in the females at necropsy compared to week 0 (45.5 fl versus 48 fl). These changes in the MCV were not associated with any changes in the packed cell volume. No abnormalities were noted in the serum chemistry parameters evaluated at the time of necropsy. At gross postmortem 'examination, the only remarkable lesion was a green, semisolid exudate in the right frontal sinus of one cat.

It was concluded that daily subcutaneous injection of butorphanol at a dosage of 2 mg/kg for one week, 4 mg/kg the following week, and 8 mg/kg the following

week, (5 to 20 times the recommended dose of 0.4 mg/kg) is without toxic effects in cats other than irritation at the injection site. Dosages of 16 mg/kg/day (40 times the recommended dosage), are associated with side effects of incoordination, salivation, or mild convulsions, signs believed to represent the toxic clinical syndrome of butorphanol overdosage in the cat.

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in cats, which are non-food animals. Human safety relative to possession, handling, and administration: no special caution statement needed.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Torbugesic(R)-SA (butorphanol) Veterinary Injection (2 mg/mL). when used under labeled conditions of use is safe and effective. The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine when an analgesic is required in the cat and because the drug is administered by subcutaneous injection.
Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(ii)), this approval for nonfood producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant.

VI. LABELING (ATTACHED)

1. Package Insert
2. 10 mL Vial Label

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.

APPENDIX I Description of Cats Treated With Butorphanol (0.4 mg/kg) In Field Trial #1 (page 10 of FOI Summary)

Case	Diagnosis	Weight (lbs)	Age Y=Years M=Months	Sex	Response	Onset of Analgesia (minutes)	Duration of Analgesia (hours)	Adverse Reactions
2	thyroid sugery	7	12Y	F	Good	20	4.5	
3	cast./declaw	10	8M	M	Excellent	20	6	M, P
5	abscess	13.5	5Y	M	Poor			
6	abscess	3.5	4M	F	Excellent	10	4	
7	fx ilium	17.4	11Y	F	Poor			
12	abscess	12	4.5Y	M	Excellent	25	8	P
15	trauma	7.25	8M	F	Poor			
19	abscess	9.75	18M	M	Poor			
21	cellulitis	10.5	1-2Y	M	Good	25	.25	S
22	fx leg	5.5	4.5M	M	Excellent	15	3.5	
23	spay	6	10M	F	Poor			
26	abscess	9.5	10M	M	Excellent	20	4-5	D, M
30	spay/declaw	6	10M	F	Excellent	8-10	6-8	M
31	fx leg	7.5	6M	F	Fair	23	1	
32	hit by car	9.5	10Y	F	Poor	25	1.5	
33	fx hip	6	5.5M	M	Poor			
35	spay/declaw	5	6M	F	Excellent	20	4	
36	declaw	9	4Y	M	Excellent	10-15	6	
38	fx femur	10	9M	M	Fair			
40	declaw	9.6	7M	M	Excellent	20	2.5	
41	declaw	4.2	6M	F	Poor			
42	declaw	9	1Y	F	Excellent	10	4	
44	spay/declaw	9	2Y	F	Good	20	6	M, P
45	declaw	7	6M	F	Excellent	15	5	P
48	abscess	8	8Y	F	Excellent	15	none given	
49	joint pain	11	9Y	M	Good	15	4.75	
50	declaw	12	7Y	M	Poor			
52	leg trauma	8	11Y	F	Poor			
53	flush bladder	11.5	6Y	M	Excellent	7.5	5-6	D
57	declaw	9.75	5Y	F	Poor			
59	declaw	6	5M	M	Excellent	10	2	P
61	spay/declaw	6	6M	F	Fair	25	1	
62	fx leg and tail	9	4-5Y	M	Good	15-20	3	

M=Months
P = pain on injection M = mydriasis D = disorientation S = sedation

APPENDIX II Description of Cats Treated With Butorphanol (0.4 mg/kg) In Field Trial #2 (page 16 of FOI Summary)

Case	Diagnosis	Weight (lbs)	Age Y=Years M=Months	Sex	Response	Onset of Analgesia (minutes)	Duration of Analgesia (hours)	Adverse Reactions
31-3	declaw	5	5M	M	Poor			
31-6	declaw	9	4Y	M	Fair			
31-7	hit by car	10	3Y	M	Good	17	6-7	
31-10	declaw	5	5M	M	Poor			
32-2	declaw	7	8Y	M	Good	2	2	
32-3	declaw	3	4M	F	Poor			
32-4	declaw	9	8M	M	Good	15	2	
33-1	declaw	15	10M	M	Excellent	20	3	
33-3	declaw/spay	7.5	6M	F	Poor			
33-4	declaw/spay	5.5	8M	F	Excellent	35	2.5	
33-8	declaw/spay	6.5	5Y	F	Excellent	20	3.5	
33-10	declaw/cast.	8	7M	M	Excellent	25	4	
34-1	declaw	9	1Y	F	Good	25	4-5	P
34-2	fx paw	12	1Y	M	Excellent	8	1	
34-3	declaw	16	3Y	M	Excellent	15-18	5-6	
34-5	fx femur	8	3Y	F	Good	8-10	6	
34-6	hit by car	6.5	1Y	F	Good	8-10	2	
35-1	abscess	11	3Y	M	Fair			
36-1	ear problem	10	15Y	M	Good	15	3.5	
36-2	bone tumor sx	12.5	9Y	M	Excellent	10	5	
36-6	trauma	4.4	5M	F	Good	30	4-5	
36-7	hit by car	6.4	3Y	F	Excellent	10-15	4-5	
36-9	pelvic trauma	11	3Y	M	Good	20	5	
37-3	catheterization	10.6	Adult	M	Excellent	15	4	
37-4	declaw	7.4	8M	M	Poor			
37-6	stifle pain	9.2	17Y	F	Poor			
37-8	bone sx	11	11Y	F	Poor			P
37-10	declaw	6.4	11M	F	Fair	20	2	
39-2	declaw	10	10M	M	Excellent	12-15	6	P
39-4	declaw	9	6Y	F	Excellent	12-15	6	
39-5	declaw	5	3.5Y	F	Excellent	12-15	6	P
39-7	declaw	6.5	10M	F	Excellent	8-10	6	
39-8	declaw	7.5	2Y	M	Excellent	10-12	6	
40-1	shoulder exam	3.8	4M	F	Excellent	20	6	
40-6	declaw	7.4	6M	M	Excellent	15	4	M
40-7	declaw	7.4	6M	M	Good	20	4	P, M, D
40-9	catheterization	9.4	4.5Y	M	Good	20	1	P
40-10	swollen leg	7.2	2Y	M	Excellent	20	2	
41-1	declaw	10.1	1Y	M	Fair	15	5	
41-4	abscess	9.4	1.5Y	F	Excellent	15-20	5	

M=Months

P = pain on injection M = mydriasis D = disorientation S = sedation