Date of Approval: December 27, 2001

FREEDOM OF INFORMATION SUMMARY

POSILAC 1 STEP®
(sometribove zinc suspension)

For Use in Healthy Lactating Dairy Cows
To Increase Production of Marketable Milk

Sponsored by Monsanto Company

TABLE OF CONTENTS PAGE

FREEDOM OF INFORMATION SUMMARY

1. General Information

a. File Number	NADA 140-872
b. Sponsor:	Monsanto Company 800 North Lindbergh Blvd. St. Louis, Missouri 63167 Drug Labeler Code: 059945
c. Established Name:	Sometribove zinc suspension
d. Proprietary Name:	POSILAC 1 STEP®
e. Dosage Form:	Prolonged-release injectable
f. How Supplied:	Single-dose syringes in 25 or 100 count boxes
g. How Dispensed:	Over-the-counter (OTC)
h. Amount of Active Ingredients:	Each single-dose syringe contains 500 mg sometribove zinc.
i. Route of Administration:	Subcutaneous injection. Recommended sites include the neck area, the postscapular region (behind the shoulder), or in the depression on either side of the tailhead.
j. Species/Class:	Lactating dairy cows
k. Dosage:	Inject one syringe of POSILAC 1 STEP® every 14 days beginning during the 9th or 10th week (57 - 70 days) after calving and continue until the end of lactation.
l. Pharmacological Category:	Hormone
m. Indications:	For use in healthy lactating dairy cows to increase production of marketable milk.

n. Effect of Supplements: This FOI Summary describes the basis for a labeling change instructing users to inject POSILAC 1 STEP® subcutaneously, with no restriction on injection site. Three injection sites are recommended: the neck area, the postscapular region, or the depression on either side of the tailhead.

This Summary also describes the basis for CVM's November 4, 1997, approval of a previous supplement to this NADA. That approval changed labeling to: allow injections to start in the 10th week of lactation in addition to the originally approved 9th week; remove the cautions for increased twinning, cystic ovaries, and uterine disorders; and modify the original caution of higher incidence of retained placenta "following subsequent calving" to just a higher incidence of retained placenta.

Throughout the Freedom of Information (FOI) Summary, the term "sometribove" is used to represent the formulated drug product, POSILAC 1 STEP® (sometribove zinc suspension).

2. Dosage Rationale

These approvals do not affect this section of the FOI Summary for the original approval. Refer to the FOI Summary dated November 5, 1993.

3. Effectiveness

Neck Versus Postscapular Subcutaneous Administration Study (Study 98-003)

A study was conducted to evaluate the effectiveness and animal safety of sometribove given by subcutaneous injection in the neck area.

Investigator and study location:

Chuck Heird, Ph. D.
Valley View Dairy
Mesquite, New Mexico

An objective of this study was to determine whether the milk production response of dairy cows administered sometribove subcutaneously in the neck area is similar to that of cows injected in the postscapular region. Equivalence was defined as 90% confidence that there was less than a 30% difference between the responses. Another objective of this study was to determine whether injection site reactions at the neck area are an animal safety concern.

MATERIALS AND METHODS

Animals

The study included 120 primiparous (first lactation/parity) and 120 multiparous (second or greater lactation/parity) Holstein cows. Cows ranged from 56 to 119 days postpartum, or "days in milk (DIM)," at the start of treatment. They were free of metabolic disorders, clinical mastitis, and signs of other diseases at the time of selection. Cows had not been administered sometribove during the lactation previous to the study, nor were they given sometribove in the current lactation prior to the start of this study.

Treatment Assignment

Cows were grouped into blocks based on parity (multiparous or primiparous) and days in milk (56 to 85 DIM or 86 to 119 DIM) and assigned to the study two weeks before the first injection. The treatments were arranged as a randomized complete block design, with 40 or 80 cows in each of the four treatment groups (Table 1).

Table 1. Number of Cows Starting Treatment. Study 98-003.

Treatment	**Injection Site**	**Number of Cows**
Excipient	Postscapular	20 primiparous
		20 multiparous
Excipient	Neck	20 primiparous
		20 multiparous
Sometribove	Postscapular	40 primiparous
		40 multiparous
Sometribove	Neck	40 primiparous
		40 multiparous

Treatments

Cows were given sometribove (500 mg) or excipient by subcutaneous injection every 14 days for 6 injection cycles, i.e., injections occurred on study days 0, 14, 28, 42, 56, and 70. Injections started at approximately 86 DIM (range of 56 to 119 DIM) and continued until a cow completed the study, or was removed from the study for health problems, whichever occurred first.

The sometribove and excipient were supplied as pre-filled syringes. Injections were made subcutaneously and alternated between the left and right sides of the cows. For cows treated in the postscapular region, injections were given in the top, middle, and bottom areas behind the shoulder. Cows treated in the neck area were injected in the intersection of the top of the shoulder and neck, the intersection of the front of the neck and the head, and the intersection of the bottom of the shoulder and neck. Thus, there were six, unique injections sites for each cow.

Injections were given at a consistent time of day across the six injection cycles. Any surface debris at the injection site was removed at the time of injection.

Cattle Management and Feeding

The milking, health, reproduction, housing, lighting, and other routine herd management practices were not altered for this study. Cows were milked three times daily at approximately 8-hour intervals. A common total mixed ration (TMR) was fed throughout the study. The chemical and nutrient composition of the TMR was consistent with the 1989 National Research Council (NRC) recommendations for lactating dairy cows at this stage of lactation (56 to 119 DIM), body condition score (~3.0), and milk production level.

Milk Weights and Milk Discard

Weight of total milk yield of every study cow at every milking was recorded from 14 days before the first sometribove or excipient injection to 14 days after the last injection, or to the last day of lactation if the cow was removed from the study, whichever occurred first. Cows that experienced health disorders (e.g., mastitis, lameness, metabolic disorders) that required therapy for treatment were removed from the milking herd and housed in a hospital pen during recuperation. Milk weights were not recorded for a cow on the days it was housed in the hospital pen.

Body Condition Score

Body conditions scores (BCS) were recorded on Day -7 (i.e., during the 14-day pretreatment period) and on Day 91 (i.e., at the end of the study) on a five-point scale (1 = very thin to 5 = obese) in 0.25 unit increments. Body condition was scored only to confirm that cows were in normal condition. The BCS among treatment groups ranged from 3.03 to 3.09 for the pretreatment period, and from 3.02 to 3.09 at the end of the treatment period, which were considered normal condition scores for cows at these stages of lactation.

Injection Site Reactions

Each injection site for every cow was scored every 7 days for 28 days, or until the injection site score was 0, whichever occurred first. Injection sites were scored

using the following system: 0 = no visible swelling; 1 = a visible swelling <10 cm in the longest surface dimension and/or <1 cm in height; 2 = a visible swelling of 10 to 16 cm in the longest surface dimension and/or 1 to 2 cm in height; and 3 = a visible swelling >16 cm in the longest surface dimension and/or >2 cm in height.

DATA HANDLING

Milk Yield Data

Milk yield data were sometimes missing because of mechanical failure or when a cow was housed in the hospital pen. If a cow's milk yield data were missing for at least one milking time on more than three days in a week, the data for that 2-week injection cycle were omitted from the milk yield analysis. Cows that had missing milk yield data for at least one milking time on more than three days in a week during the pretreatment period, and cows that did not have complete milk yield data for at least four injection cycles were excluded from the analysis of milk yield.

All data for one primiparous cow (#7598) assigned to the Excipient-Postscapular treatment group, and one primiparous cow (#7644) assigned to the Excipient-Neck treatment group, were excluded because they each had only three functional quarters. Milk production data for three multiparous cows assigned to the Sometribove-Postscapular treatment group were excluded because of insufficient milk yield data during the pretreatment period (#4467; mastitis), fewer than four cycles of milk yield data (#5714; chronic mastitis), and early removal from the study because of chronic lameness (#6652). One primiparous cow (#7774; mastitis) assigned to the Sometribove-Neck treatment group was excluded because of insufficient milk yield data during the pretreatment period and fewer than four cycles of milk yield data during the treatment period.

The 25 cows that had one or two cycles of milk yield data excluded from the analysis, and the reasons that caused cycles to be excluded, are given in Table 2.

Table 2. Cows with Milk Yield Data Excluded from Analysis. Study 98-003.

Treatment Group	Parity[a]	Cow ID	Cycle(s) Omitted[b]	Reason
Excipient-Postscapular	M	3389	6	Lameness
	M	7075	3	Mastitis
	M	8739	2, 3	Mastitis
Excipient-Neck	M	4956	4	Ketosis
	M	6716	2, 5	Mastitis
Sometribove-Postscapular	M	5377	2	Mastitis
	M	5662	6	Mastitis
	M	6894	2	Mastitis
	M	7066	5, 6	Mastitis
	M	8751	6	Mastitis
	M	8854	2	Mastitis
	P	7554	5	Mastitis
	P	7667	4	Lameness
	P	7686	1	Mastitis
	P	7750	6	Mastitis
	P	7800	4	Mastitis
Sometribove-Neck	M	5067	6	Lameness
	M	6086	3, 4	Mastitis
	M	6447	6	Mastitis
	M	8077	6	Mastitis
	M	8326	6	Diarrhea and indigestion
	M	8438	4, 6	Mastitis
	M	8824	6	Mastitis
	P	7610	1, 2	Mastitis
	P	7650	6	Mastitis

[a] P = Primiparous; M = Multiparous.
[b] Two-week injection cycle(s) excluded from the analysis.

Calculation of Average Daily Milk Yield

Every cow's milk yield values recorded during the 2-week pretreatment period and during the 6-injection cycle treatment period were reduced to a mean value for the respective periods prior to statistical analysis.

For the 2-week pretreatment period, daily milk yield averages were first computed for each of the two weeks. The average daily yield for a week was computed by summing the milk yield values within a milking time (e.g., all 7 values for the 0600 milking time) within a week, and then dividing the sum by the number of non-missing values for that milking time. The average values for each of the three milking times within a week then were summed to calculate the average daily yield for the week. The two weekly values then were averaged to compute the average daily milk yield for the 2-week pretreatment period. The final value was used for calculating the covariate in the statistical analysis.

For the treatment period, a similar approach was used for each of the six injection cycles. The average daily yields for the six injection cycles then were averaged to represent the average daily milk yield for the entire treatment period. That value was used in the statistical analysis for average daily milk yield.

Injection Site Reaction Data

Injection site data for one primiparous cow (#7598) assigned to the Excipient-Postscapular treatment group, and one primiparous cow (#7644) assigned to the Excipient-Neck treatment group, were excluded from analysis because those cows were removed from the study (see above) prior to their first injection site score. The three multiparous cows (#4467, #5714, and #6652) assigned to the Sometribove-Postscapular treatment group and the primiparous cow (#7774) assigned to the Sometribove-Neck treatment group that had been excluded from the milk yield analysis (see above) were included in the analysis for injection site reactions. However, cow #6652 contributed data for only two injection sites because it was removed from the study before its third injection site was scored (see above).

If any of a cow's injection sites reached a score of "0" prior to 28 days of observation, the site was assigned a score of "0" for the remaining weekly observations. The two injection sites for cow #6652 reached a score of "0" before the cow was removed from the study, and so those sites were assigned a score of "0" for the remaining observations. Thus, the average value for each injection site was calculated by using a common denominator (i.e., 4 injection site observations).

STATISTICAL ANALYSIS

Milk Yield Data

The response variable was average daily yield of milk for the treatment period. To qualify the neck as a site of injection, the milk production responses (difference from control) of cows administered sometribove in the neck and postscapular regions must be equivalent.

The 2-week pretreatment average daily milk yields expressed as a deviation from the block by parity mean were used as covariates. The initial model terms in the analysis were treatment, parity, treatment*parity, block(parity), treatment*block(parity), and the covariate. The treatment*parity interaction was not significant ($P<0.05$); thus, the data were not subjected to separate parity analyses. The two excipient groups were combined in the final analysis, which was weighted by the number of cycles contributed by each cow.

Equivalence for the neck versus postscapular region was evaluated by constructing a 90% confidence interval on the difference of average daily milk yield between the neck and postscapular treatment groups and dividing the confidence limits by the difference of average daily milk yield between the postscapular and the combined excipient treatment groups. The lower limit of

>-0.30 and the upper limit of <+0.30 defined equivalence (i.e., less than a 30% difference between the neck and postscapular responses).

Injection Site Reactions

Injection site scores were analyzed as a repeated measures design. Whole plot terms included: injection location (i.e., neck and postscapular), drug (i.e., sometribove and excipient), and drug*location interaction. The subplot terms included injection site (i.e., the six possible injection sites on each cow), and the sub-subplot term was the week of observation for any particular site.

RESULTS

Average daily milk yield for the combined excipient groups was 35.3 kg/day. For the sometribove groups the average daily milk yield was 39.0 kg/day for cows injected in the postscapular region and 39.4 kg/day for cows injected in the neck (Table 3). The 90% confidence interval (-0.359, 1.088) for the difference between postscapular and neck injection, divided by the least squares mean for the difference between sometribove-postscapular and excipient groups (3.76 kg/day), resulted in limits (-0.095, 0.289) that met the equivalence requirement (-0.30, +0.30).

Table 3. Milk Yield of Cows given Sometribove or Excipient in the Postscapular or Neck Region. Study 98-003.

Treatment Group	Number of Cows	Milk Yield[a] (kg/d)	Difference from Excipient[b] (kg/d)
Excipient (Postscapular + Neck)	78	35.3 ± 0.31	0.0
Sometribove-Postscapular	77	39.0 ± 0.31	3.8
Sometribove-Neck	79	39.4 ± 0.31	4.1

[a] Least squares means ± standard error.
[b] Calculated before rounding treatment means.

Injection site reaction data are discussed in Section 4.a.

CONCLUSIONS

There was no difference in the average daily milk yield response in dairy cows administered sometribove by subcutaneous injection in the postscapular region versus the neck area. The results of the study demonstrated that subcutaneous injection of sometribove in the neck area is effective for the intended use.

4. Target Animal Safety

The Target Animal Safety of sometribove was established in the original NADA approval for subcutaneous injections of 500 mg every 14 days in the postscapular and tailhead regions, starting during the 9th week postpartum (see FOI Summary dated November 5, 1993).

The following sections summarize studies providing additional animal safety data for sometribove. Label caution statements were changed as a result of these studies to more accurately describe the animal safety effects of sometribove.

a. Neck Versus Postscapular Subcutaneous Administration Study (Study 98-003)

As concluded in Section 3 of the current FOI Summary, subcutaneous injection of 500 mg of sometribove every 14 days in the neck area results in a milk yield response similar to subcutaneous injections of 500 mg every 14 days in the postscapular region. Thus, with the exception of injection site reactions, the target animal safety of sometribove when injected subcutaneously in the neck is expected to be similar to subcutaneous injections in the postscapular and tailhead regions.

The second objective of Study 98-003 was to determine whether injection site reactions in the neck area are an animal safety concern.

The descriptions of injection sites, injection site scoring, and analysis of injection site scores were described in Section 3.

RESULTS

Mean injection site scores were greater in cows given sometribove compared with cows given excipient (0.201 versus 0.038; $P<0.001$; Table 4). Cows given sometribove in the neck area had significantly greater injection site scores compared with cows given sometribove in the postscapular region (0.230 versus 0.173; $P=0.002$; Table 4). Cows administered sometribove in the neck had larger injection site scores initially than did cows given sometribove in the postscapular region. However, injection site reactions for both regions given sometribove subsided to an average score of "zero" by 28 days post-injection (data not shown).

Table 4. Injection Site Scores of Cows given Sometribove or Excipient in the Postscapular or Neck Region.[a] Study 98-003.

Treatment Group	Number of Cows[b]	Injection Site Score[c]	Standard Error	
Excipient-Postscapular	39	0.042	0.018	
Excipient-Neck	39	0.035	0.018	
Sometribove-Postscapular	80	0.173	0.013	
Sometribove-Neck	80	0.230	0.013	
Main Effect				
Excipient	78	0.038	0.013	
Sometribove	160	0.201	0.009	
Postscapular	119	0.107	0.011	
Neck	119	0.132	0.011	
Differences				**P value**
Sometribove vs. Excipient	160 vs. 78	0.163	0.016	<0.001
Neck vs. Postscapular	119 vs. 119	0.025	0.016	0.121
Neck vs. Postscapular (for Excipient)	39 vs. 39	-0.007	0.026	0.788
Neck vs. Postscapular (for Sometribove)	80 vs. 80	0.057	0.018	0.002

[a] Injection sites were scored weekly until the score was "0". Mean injection site score is the mean to day 28 with zeros assigned to weeks after a score of "0".
[b] Number of cows contributing injection site scores.
[c] Least squares means.

CONCLUSIONS

Cows given sometribove in the neck area had larger injection site reactions initially than did cows given sometribove in the postscapular region, but injection site reactions for both regions subsided by 28 days. The difference in reactions among regions is small enough such that animal safety of cows injected with sometribove in the neck area is not compromised. However, product labeling indicates that larger swellings may occur at the injection site of cows given sometribove in the neck region compared to the postscapular or tailhead regions.

b. 28-Herd One-Lactation Post-Approval Monitoring Program Study (PAMP Study)

A study was conducted at 28 separate U.S. locations to evaluate the effectiveness and target animal safety of sometribove (500 mg subcutaneously every 14 days for one lactation) under actual conditions of use as part of a Post-Approval Monitoring Program. The same study protocol was used at each location, with minor variations to allow for differences in management practices.

Investigator: Robert J. Collier, Ph.D.
Monsanto Company
St. Louis, Missouri

An objective of this study was to evaluate the effect of sometribove on animal health and reproduction on commercial dairy farms throughout the U.S. Data from this study and studies submitted to the original NADA for sometribove were reviewed to determine whether approved labeling for the product was accurate. Based on this review, a supplemental NADA was approved November 4, 1997, that changed label caution statements to more accurately describe the animal safety effects of sometribove.

MATERIALS AND METHODS

Locations

The study was run at 28 commercial dairy herds located in major dairy producing states in four geographic regions of the United States (Upper Midwest, Northeast, Southeast, and West; see Table 5). At least six herds were selected per region. At least one "small" herd (60 or fewer lactating cows) was also selected in each region. Jersey cows were used on the study at two of the locations (Herd IDs SC and WE; Table 5), and Holsteins were used on the study at the remaining herds.

Herds selected for the study had a regular herd health program, reliable health records, sound programs for nutrition and milking, and a minimum rolling herd average (RHA) or herd 305-day mature equivalent milk yield: 14,000 lb (6350 kg) for herds milking 2 times per day; 17,000 lb (7700 kg) for herds milking 3 times per day; and 19,000 lb (8600 kg) for herds milking 4 times per day. Herds had culling rates below 40% and an average bulk tank somatic cell count (SCC) less than 300,000 cells/ml. Each herd also had sufficient cows available to start treatment within six months after the start of the study (or 12 months for small herds). Information on each herd is provided in Table 5.

Table 5. Herd Information. PAMP Study.

Herd ID	State	Number of cows: In Herd	Number of cows: Milking in Herd	Number of cows: On Study[a]	Times Milked per Day	RHA[b] (lb)	Herd ME305[c] (lb)
Midwest							
MA	MN	406	340	38	3	25920	23400
MB	MN	199	185	22	3	24900	23500
MC	WI	145	60	20	2	22050	24350
MD	WI	1000	875	52	3	22900	25160
ME	WI	310	200	54	3	25670	26640
MF	WI	310	155	53	3	26200	28430
MG	WI	185	155	47	2	22670	24800
Northeast							
NA	NJ	436	199	53	2	25440	.
NB	NJ	1000	380	56	3	24230	23000
NC	PA	410	350	52	2	21080	23800
ND	NY	150	125	48	2	19570	.
NE	NY	530	450	54	3	23500	.
NF	NY	604	273	52	3	25750	23880
NG	PA	76	40	12	2	18810	20950
NH	PA	45	42	14	2	24150	24500
Southeast							
SA	SC	55	53	18	2	.	16800
SB	FL	690	650	50	3	20500	19650
SC	SC	369	316	49	2	14100	15150
SD	SC	125	110	56	2	20000	21630
SE	FL	468	396	48	4	22130	22380
SF	FL	424	363	41	2	17650	20230
West							
WA	ID	612	525	67	3	25000	23740
WB	CO	436	386	49	3	23820	26670
WC	CO	1600	1400	48	3	22000	23500
WD	CO	890	415	48	3	23830	.
WE	ID	107	47	15	2	15390	17120
WF	CA	1270	1130	49	2	19900	23220
WG	CA	3380	1740	48	2	20630	23620
Total = 28 herds				**1213 cows started treatment**			

[a] Began sometribove or excipient treatment.
[b] Rolling herd average milk yield (not available at all locations).
[c] Herd's 305-day mature equivalent milk yield (not available at all locations).

Animals

Primiparous and multiparous dairy cows were used at each study location. Cows in their first through eighth lactation were included, although most of the study cows (84%) were in their first through third lactation. Cows ranged from 57 to 70 days in milk (DIM) at the start of treatment. Each cow's estimated lactation yield before the start of the study was not less than 4000 lb below the herd's RHA. Cows were free of signs of health or conformation problems and had four functional quarters at the start of treatment. Their body condition was appropriate for early lactation. The cows were acclimated to the herd facilities. Each cow had a minimum of two monthly DHIA (or equivalent) records of milk yield and SCC before starting treatment.

Treatment Assignment

A total of 1213 cows began treatment. The study was run as a randomized block design. Treatments consisted of 0 or 500 mg sometribove every 14 days. Within each herd, cows were blocked by parity (multiparous or primiparous) and calendar date, and cows within blocks were randomly assigned to one of the two treatment groups. Individual treatment assignments of cows in each herd were not identified to the herd's veterinarian or farm personnel.

Treatments

Cows were administered sometribove (500 mg) or excipient (0 mg) by subcutaneous injection in the post-scapular region or in the depression on either side of the tailhead according to instructions provided on the commercial product labeling (POSILAC 1 STEP®). Within study location, treatment injections occurred on the same day of the week every 2 weeks and at approximately the same time of day. Injections started at 57 to 70 DIM (i.e., 9^{th} or 10^{th} week postpartum) and continued until a cow was dried off, was 400 DIM, or was culled from the herd, whichever occurred first. Pregnant cows were monitored through calving.

The sometribove and excipient were supplied as pre-filled syringes. The syringes were identified only as "A" or "B" and did not specify whether they contained sometribove or excipient.

Cattle Management

The milking, health, feeding, and other general management of cows were not altered for this study except where necessary to collect data specified in the protocol.

Normal culling practices were followed by all herds. Before removing a cow from the study, the herd veterinarian or clinical investigator was contacted. Reasons for removal were documented. If the culling was due to health problems, the cow was examined by the veterinarian, and clinical conditions were documented. Cows that died while on study or that required euthanasia because they were moribund were necropsied by the attending veterinarian. All available practical means were used to determine the cause of any illness, death, or injury.

Health and Production Observations

Each study cow's milk production and SCC were recorded using monthly DHIA (or equivalent program) records. These records were collected from calving through the end of the study.

All study cows were observed daily for abnormal health conditions beginning at least two weeks before the start of treatment and continuing two weeks after their

last injection. Any health-related observations were recorded daily. For cows that were clinically ill, additional health parameters were recorded such as body temperature, appetite, or activity.

The incidence of clinical mastitis was also recorded. Clinical mastitis was defined as the presence of abnormal milk, e.g., flakes, clots, strings, clumps, or discoloration from blood or serum. Other signs of mastitis were also recorded, such as swelling, heat, or pain in the affected quarter(s), depression, anorexia, or reduced milk yield.

Each day that sometribove or excipient was administered at a study location, the herd veterinarian observed all study cows and recorded any clinical observations.

Each location recorded all medications and therapies given to study cows.

Reproduction records were maintained according to each herd's practice. Cows were bred via artificial insemination except at the WF herd, where cows were bred by bulls. Only pregnancy palpation records were available for the WF herd.

DATA HANDLING

Of the 1213 cows starting treatment in the PAMP Study (Table 5), 85 were excluded from data analysis due to protocol deviations, such as not meeting selection criteria or being assigned to the wrong parity group. Data from the remaining 1128 cows (709 multiparous and 419 primiparous) were included in analyses (Table 6).

Table 6. Cows Included in Analysis. PAMP Study.

	Dose of Sometribove (every 14 days)		
Parity	0 mg	500 mg	Totals
Primiparous	209	210	419
Multiparous	356	353	709
		Total Cows =	1128

Results from the PAMP Study and studies included in the original NADA approval were evaluated to determine whether approved labeling for POSILAC 1 STEP® was accurate.

Studies submitted to the original NADA 140-872 are described in the FOI Summary dated November 5, 1993. Table 7 provides a brief summary of the original NADA studies evaluated in conjunction with the PAMP Study data.

Table 7. Summary of Key Original NADA 140-872 Studies Evaluating Effectiveness and Target Animal Safety.

4 Dose-SC	**Multi-location SC Dose Response Clinical Study** Conducted at 4 separate U.S. locations. 109 primiparous and 145 multiparous cows injected subcutaneously (SC; postscapular) with either 0, 250, 500, or 750 mg sometribove every 14 days for 1 lactation starting 60 ± 3 DIM.
IM/SC Bridging	**Intramuscular Versus Subcutaneous Route of Injection Study** Conducted at 1 U.S. location. 21 primiparous and 43 multiparous cows injected either SC (pre- or postscapular) or intramuscularly (IM; hamstring) with either 0 or 500 mg sometribove every 14 days for 1 lactation starting 60 ± 3 DIM.
Dose-IM	**Intramuscular Dose Titration Study** Conducted at 1 U.S. location. 28 primiparous and 57 multiparous cows injected IM (hamstring) with either 0, 250, 500, or 750 mg sometribove every 14 days for 1 lactation starting 60 ± 3 DIM.
Single Dose-IM	**Multi-location Intramuscular Single Dose Study** Conducted at 4 separate U.S. locations. 92 primiparous and 272 multiparous cows injected IM (hamstring) with either 0 or 500 mg sometribove every 14 days for 1 lactation starting 60 ± 3 DIM.

For the evaluation of animal safety variables, including reproduction, data from each study were first analyzed separately. Reproduction data from studies using the IM route of injection were also pooled for the 0 and 500 mg doses (including the IM injected cows from the IM/SC Bridging Study) and reanalyzed as the **"IM-Pooled Study."** Animal safety data from all 4 of the studies listed above were also pooled for the 0, 250, 500, and 750 mg doses and reanalyzed as the **"IM-SC Pooled Study."**

RESULTS

Target animal safety results for the PAMP Study were consistent with those of the original NADA approval with the exception of effects on twinning rates, cystic ovaries, uterine disorders, and retained placenta. Also, cows in the PAMP Study started treatment over a two-week period postpartum, compared to a one-week period for the original NADA studies. These differences in animal safety effects and treatment start time resulted in changes to product labeling.

Treatment Start Time

Treatment of cows with sometribove in the original NADA studies began during the 9th week postpartum, whereas treatment in the PAMP Study began during the 9th or 10th week postpartum. There were no obvious differences in effectiveness or animal safety of sometribove in cows starting treatment in the 10th versus the 9th week postpartum of the PAMP Study. Also, users of sometribove can schedule injection of cows on their dairy farms once every two weeks if treatment can start over a 2-week period postpartum.

Conclusion

The November 4, 1997, supplemental NADA approval changed product labeling to indicate that sometribove treatment should begin during the 9th or 10th week after calving. Labeling has been further changed to add "57 - 70 days" in parentheses between "9th or 10th week" and "after calving" to more clearly define when treatment should start.

Twinning

Labeling for sometribove resulting from the original NADA approval indicated that treated cows may have increased twinning rates (i.e., rates of multiple births). However, increased twinning was observed only in cows given sometribove by IM injection, not those injected SC (Table 8).

Table 8. Rate of Multiple Births (full-term pregnancies). Original NADA Studies[a].

Parity	Dose of Sometribove (every 14 days)				P value
	0 mg	250 mg	500 mg	750 mg	
IM-Pooled Study (conceived days 60-170 of lactation)[b]					
Primiparous	2.9% (1/34[c])		20.8% (5/24)		0.016
Multiparous	1.2% (1/86)		13.6% (11/81)		0.003
4 Dose-SC Study (conceived days 60-180 of lactation)[d]					
Primiparous	5.0% (1/20)	5.9% (1/17)	5.3% (1/19)	10.0% (2/20)	0.560
Multiparous	13.3% (4/30)	4.8% (1/21)	9.5% (2/21)	13.6% (3/22)	0.936

[a] Source: Freedom of Information Summary, NADA 140-872, dated November 5, 1993, Table 63.
[b] Cochran-Mantel-Haenszel Chi-square test for difference between control and treated cows.
[c] Number of cows with multiple births (full-term pregnancies) divided by number of cows with full-term pregnancies.
[d] Linear trend in proportion across dosage levels (Cochran-Armitage).

In light of these results, the 4 Dose-SC Study of the original NADA as well as the PAMP Study were reviewed to determine whether cows treated with sometribove by SC injection had increased twinning rates compared to control cows. Twinning data for the 0 and 500 mg doses of the 4 Dose-SC and PAMP Studies were pooled and analyzed. The incidence of multiple births in primiparous or multiparous cows was not affected by sometribove treatment (Table 9).

Table 9. The Effect of SC Injected Sometribove on Incidence of Multiple Births. Pooled 4 Dose-SC and PAMP Studies.

Parity	Percent of Cows with Multiple Births (number of cows with multiple births/number of cows)		Probability[a]	
	Dose of Sometribove (every 14 days)			
	0 mg	500 mg	A	B
Primiparous	12.3 (16/130)	6.9 (9/130)	0.611	0.113
Multiparous	9.0 (20/222)	9.7 (18/186)	0.579	0.915

[a] A: Probability for testing homogeneity of odds ratios across studies (Breslow-Day Statistic).
B: Difference between doses for data pooled studies (Cochran-Mantel-Haenszel Chi-square test).

Conclusion

Twinning rate was not increased in cows given sometribove by SC injection. Sometribove is only approved for SC injection, and so the November 4, 1997, supplemental NADA approval removed the "increased twinning" caution from product labeling.

Cystic Ovaries

Labeling for sometribove from the original NADA approval indicated that treatment was associated with increases in cystic ovaries. The basis for this label caution was a significant increase in cystic ovaries for sometribove-treated primiparous cows in the 4 Dose-SC Study and sometribove-treated multiparous cows in the IM-Pooled Study ($P<0.10$; see Table 10). The increase in cystic ovaries in sometribove-treated cows appeared more prominent for cows treated IM compared to SC injections.

The effect of sometribove treatment on the incidence of cystic ovaries in the PAMP Study was examined in daily observations and biweekly veterinary observations. Cystic ovary data recorded during daily observations were analyzed, but there were no recordings of cystic ovaries in the veterinary observations. The incidence of cystic ovaries was not affected by sometribove treatment for either primiparous or multiparous cows in the PAMP Study (Table 10).

Table 10. Effect of Sometribove on Incidence of Cystic Ovaries. Original NADA and PAMP Studies.

Study	Percent of Cows with Cystic Ovaries (number of cows with cystic ovaries/number of cows) Dose of Sometribove (every 14 days) 0 mg	250 mg	500 mg	750 mg	P value
Primiparous Cows					
IM-Pooled[a,b]	7.3 (3/41)		18.8 (9/48)		0.108
4 Dose-SC[a,c]	19.2 (5/26)	29.6 (8/27)	18.5 (5/27)	48.0 (12/25)	0.065
PAMP[b]	11.8 (23/195)		12.7 (25/197)		0.808
Multiparous Cows					
IM-Pooled[a,b]	14.5 (17/117)		26.2 (34/130)		0.048
4 Dose-SC[a,c]	17.1 (6/35)	20.6 (7/34)	31.3 (10/32)	25.7 (9/35)	0.265
PAMP[b]	12.9 (42/326)		11.3 (36/319)		0.529

[a] Source: Freedom of Information Summary, NADA 140-872, dated November 5, 1993, Table 64.
[b] Difference between control and treated (Cochran-Mantel-Haenszel Chi-square test).
[c] Linear trend in proportions across dosage levels (Cochran-Armitage).

Conclusion

The incidence of cystic ovaries was not increased in cows given sometribove during the PAMP Study. There was some evidence of increased cystic ovaries associated with sometribove treatment in the original NADA studies, but this was more strongly associated with IM injection of sometribove than SC injection. Based upon the larger data set from the PAMP study, it was concluded that the incidence of cystic ovaries was not increased in cows given sometribove by SC injection. The November 4, 1997, supplemental NADA approval removed this caution from product labeling.

Uterine Disorders

Labeling for sometribove from the original NADA approval indicated that treatment was associated with increases in disorders of the uterus. The basis for this label caution was a significant increase in the proportion of cows with uterine disorders (e.g., enlarged uterus, fluid in the uterus, adhesions, etc.) for sometribove-treated multiparous cows in the IM-SC Pooled Study ($P<0.10$; Table 11). Also, days affected with uterine disorders was increased for multiparous and primiparous cows treated with sometribove in the IM-SC Pooled Study ($P<0.10$; Table 12).

The effect of sometribove treatment on the incidence of uterine disorders was reexamined for the original 4 Dose-SC Study. Also, the daily observation and biweekly veterinary observation data sets of the PAMP Study were analyzed for the incidence of uterine disorders. Disorders of the uterus were detected by rectal palpation or visual appraisal. Both the number of cows affected and days affected during the full treatment period were analyzed.

Sometribove treatment did not affect the number of cows with uterine disorders in the 4 Dose-SC and PAMP Studies (Table 11). The number of days affected with uterine disorders was increased in sometribove-treated multiparous cows in the PAMP Study for the daily observation data base, but not the veterinary observations (Table 12). However, the number and proportion of days affected with uterine disorders for the daily and veterinary observations of the PAMP Study were extremely low for control and sometribove-treated cows (<0.1%; Table 12). Thus, the clinical relevance of the significant increase for sometribove-treated multiparous cows was questionable. Also, the term "uterine disorders" included several different abnormalities, further reducing the importance of the significant effect. For example, "retained placenta," which was already addressed on product labeling, appeared to be related to some of the days of uterine disorders recorded for sometribove-treated multiparous cows (i.e., for two cows that aborted during the treatment period).

Table 11. Effect of Sometribove on Incidence of Uterine Disorders - Number of Cows Affected (Full Treatment Period). Original NADA and PAMP Studies.

Study	Percent of Cows with Uterine Disorders (number of cows with uterine disorders/number of cows) Dose of Sometribove (every 14 days) 0 mg	250 mg	500 mg	750 mg	P value
Primiparous Cows					
IM-SC Pooled[a,b]	5.7 (5/87)	2.9 (1/34)	10.5 (10/95)	11.8 (4/34)	0.159
4 Dose-SC[b,c]	3.7 (1/27)	0.0 (0/27)	10.7 (3/28)	3.7 (1/27)	0.549
PAMP[d,e]	1.4 (3/209)		1.4 (3/210)		0.980
PAMP-VET[e,f]	0.0 (0/209)		0.0 (0/210)		1.000
Multiparous Cows					
IM-SC Pooled[a,b]	6.0 (12/201)	11.5 (6/52)	13.7 (29/212)	5.8 (3/52)	0.059
4 Dose-SC[b,c]	5.6 (2/36)	16.2 (6/37)	11.8 (4/34)	2.6 (1/38)	0.517
PAMP[d,e]	1.4 (5/356)		2.0 (7/353)		0.586
PAMP-VET[e,f]	0.6 (2/354)		0.6 (2/353)		0.987

[a] Source: Freedom of Information Summary, NADA 140-872, dated November 5, 1993, Table 81.
[b] Linear trend in proportions across dosage levels (Cochran-Armitage).
[c] Source: Original NADA 140-872.
[d] Daily observations.
[e] Difference between control and treated (Cochran-Mantel-Haenszel Chi-square test).
[f] Biweekly veterinary observations.

Table 12. Effect of Sometribove on Incidence of Uterine Disorders - Number of Days Affected (Full Treatment Period). Original NADA and PAMP Studies.

Study	Percent of Days Affected with Uterine Disorders (number of days affected/total number of days observed)				P value
	Dose of Sometribove (every 14 days)				
	0 mg	250 mg	500 mg	750 mg	
Primiparous Cows					
IM-SC Pooled[a,b]	0.0 (5/22217)	0.0 (1/9895)	0.1 (15/25094)	0.1 (6/9913)	0.025
4 Dose-SC[b,c]	0.0 (1/7475)	0.0 (0/7859)	0.1 (6/7825)	0.0 (1/7730)	0.361
PAMP[b,d]	0.0 (4/53961)		0.0 (3/55704)		0.674
PAMP-VET[b,e]	0.0 (0/3689)		0.0 (0/3825)		1.000
Multiparous Cows					
IM-SC Pooled[a,b]	0.0 (16/48138)	0.1 (15/13146)	0.1 (44/53336)	0.1 (10/13415)	0.007
4 Dose-SC[b,c]	0.0 (2/9169)	0.2 (15/9726)	0.1 (7/9131)	0.0 (3/10144)	0.569
PAMP[b,d]	0.0 (6/87075)		0.0 (17/88590)		0.021
PAMP-VET[b,e]	0.0 (2/5971)		0.0 (3/6086)		0.668

[a] Source: Freedom of Information Summary, NADA 140-872, dated November 5, 1993, Table 81.
[b] Linear trend in proportions across dosage levels, or difference between 0 and 500 mg treatment groups (Poisson regression).
[c] Source: Original NADA 140-872.
[d] Daily observations.
[e] Biweekly veterinary observations.

Conclusion

The incidence of uterine disorders was very low in the PAMP Study. The term included several types of abnormalities, further reducing its importance. It was concluded that there was no meaningful effect of sometribove treatment on the incidence of uterine disorders. The November 4, 1997, supplemental NADA approval removed this caution from product labeling.

Retained Placenta

Labeling for sometribove from the original NADA approval stated: "Also, the incidence of retained placenta may be higher following subsequent calving." The basis for this statement was an observation in the original NADA studies that monitored cows during the early subsequent lactation (approximately first 56 DIM) after the lactation of treatment. More sometribove-treated cows compared to controls tended to have retained placenta during that period (see FOI Summary dated November 5, 1993, Table 85). Analysis of the individual trials contributing to this data set via a stratified analysis (based on the Mantel-Haenszel test) confirmed these results (see discussion in FOI Summary dated November 5, 1993, Section 6.k).

The PAMP Study did not record the incidence of retained placenta at the calving following the lactation of treatment. However, as mentioned in the previous section, retained placenta contributed to the increased number of days that

sometribove-treated multiparous cows had uterine disorders during the treatment period.

Conclusion

The incidence of retained placenta may be increased in sometribove-treated cows during the treatment period as well as following the subsequent calving. The November 4, 1997, supplemental NADA approval changed the label caution statement regarding retained placenta to: "Also, the incidence of retained placenta may be higher."

5. Human Food Safety

These approvals do not affect this section of the FOI Summary for the original approval. Refer to the FOI Summary dated November 5, 1993.

6. Agency Conclusions

The data submitted in support of these supplemental NADAs satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that POSILAC 1 STEP® (sometribove zinc suspension) administered by subcutaneous injection is safe and effective for increased production of marketable milk in healthy lactating dairy cows. The neck area is acceptable as one of three recommended sites of injection. Effectiveness and animal safety of the product when starting treatment during the 10^{th} week postpartum is not different than when starting during the 9^{th} week postpartum. The rate of multiple births (e.g., twinning) is not increased in sometribove-treated cows. Also, the incidence of cystic ovaries and uterine disorders is not increased when cows are treated with sometribove. The incidence of retained placenta may be increased in sometribove-treated cows during the treatment period as well as following the subsequent calving. Product labeling has been changed to reflect these conclusions.

The Center for Veterinary Medicine has concluded that adequate directions are provided for Over-the-Counter (OTC) use of this drug product by the layperson. Label directions are accompanied by pictorial diagrams and detailed instructions in plain language. The drug is not a controlled substance. Thus, the product retains OTC status, and labeling is adequate for the intended use.

Under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670), POSILAC 1 STEP® is not eligible for generic copying because it is a drug primarily manufactured using biotechnology.

These supplemental new animal drug applications are Category II changes (21 CFR 514.106(b)(2)). The approval of these changes is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, these approvals did not require a reevaluation of the safety and effectiveness data in the parent application.

POSILAC 1 STEP® is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,013,713	May 7, 2008
5,086,041	February 4, 2009
5,411,951	February 4, 2009
5,474,980	February 4, 2009
5,595,971	February 4, 2009
5,739,108	February 4, 2009

7. Labeling

Attachments:
Package Insert
Shipper Carton
Tamper Evident Seal
Syringe
25 Count Box
100 Count Box

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

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 827-6567.