Date of Approval: September 11, 2003

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-872

POSILAC

Sometribove Zinc Suspension
Prolonged-Release Injectable
Lactating Dairy Cows

To Increase Production of Marketable Milk
in Healthy Lactating Dairy Cows

Sponsored by:

Monsanto Company

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**FREEDOM OF INFORMATION SUMMARY**

## *1. GENERAL INFORMATION:*

| | |
|---|---|
| a. File Number: | NADA 140-872 |
| b. Sponsor: | Monsanto Company<br>800 North Lindbergh Blvd.<br>St. Louis, Missouri 63167<br><br>Drug Labeler Code: 000911 |
| c. Established Name: | Sometribove zinc suspension |
| d. Proprietary Name: | POSILAC |
| 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, behind the shoulder, or in the depression on either side of the tailhead. |
| j. Species/Class: | Lactating dairy cows |
| k. Recommended Dosage: | Inject one syringe of POSILAC every 14 days. Start during the $9^{th}$ or $10^{th}$ week (57 - 70 days) after calving and continue until the end of lactation. |
| l. Pharmacological Category: | Protein hormone |
| m. Indications: | To increase production of marketable milk in healthy lactating dairy cows. |

n. Effect of Supplement: This Freedom of Information Summary describes the basis for labeling changes to modify/remove precautions pertaining to target animal safety and reproduction.

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

## *2. EFFECTIVENESS:*

### a. Dosage Characterization

This supplemental approval does not affect this section of the FOI Summary for the original approval and supplements to the original approval. Refer to the FOI Summaries dated November 5, 1993, and December 27, 2001.

### b. Substantial Evidence

This supplemental approval does not affect this section of the FOI Summary for the original approval and supplements to the original approval. Refer to the FOI Summaries dated November 5, 1993, and December 27, 2001.

## *3. TARGET ANIMAL SAFETY:*

The target animal safety of sometribove was established in the original NADA (see FOI Summary dated November 5, 1993) and supplements to the original approval (see FOI Summary dated December 27, 2001).

Effects of sometribove on animal safety for the original NADA were evaluated in part from analysis of "cow health" data. These data were based on daily health observations made by study personnel and clinical observations during periodic physical examinations made by veterinarians for all cows in the target animal safety and effectiveness studies. Also, the incidence of clinical mastitis was recorded at every milking. Effects of sometribove treatment on reproduction and calves born to treated cows were also evaluated.

To evaluate the effects of sometribove on cow health and reproduction for the original NADA, emphasis was placed on results obtained from four clinical studies where cows were managed under conditions similar to actual commercial use and dosages of sometribove were near the intended dose of 500 mg every 14

days. In these studies, sometribove and control articles were injected by either a subcutaneous or intramuscular route of administration. Statistical analysis of cow health and reproduction data included methods such as the Cochran-Armitage trend test, the Cochran-Mantel-Haenszel nonzero correlation test, Poisson regression, and residual Chi-square. These methods of analysis were limited to the narrow inference space characterized by only the conditions observed. Mixed model analyses, which were not available at the time of the original NADA approval, provide more accurate comparisons between treatments over the broad inference space of the entire population represented by study locations. Mixed model analyses are believed to be more reliable than the previously used procedures and are now typically used to analyze target animal safety data. Thus, cow health and reproduction data from clinical studies reported in the original NADA were reanalyzed using mixed model analyses.

In addition, a multi-location post-approval study was conducted after the original NADA to evaluate the effects of sometribove under actual conditions of use (see FOI Summary dated December 27, 2001, Section 4.b). Cows in this study were injected subcutaneously with either sometribove or control articles, which is the approved route of administration for the product. Cow health and reproduction data from this study were reanalyzed using mixed model analyses.

Intramuscular injection of sometribove exposes treated cows to greater concentrations of circulating bovine somatotropin than subcutaneous injection (see FOI Summary dated November 5, 1993, Section 6.c). Subcutaneous injection is the approved route of administration for this product. Thus, for some variables, data from the post-approval study were pooled with data from cows in the original NADA studies that were injected subcutaneously and analyzed using mixed model analyses. Pooling these data emphasized results from cows treated with sometribove using the approved route of administration.

Results of these analyses were used to modify label caution statements to more accurately describe animal safety and reproduction effects of sometribove.

**a. Study Summarization**

Original NADA Studies

Cow health and reproduction data from four clinical studies evaluated in the original NADA were reanalyzed using mixed model analyses. Primiparous (first lactation/parity; heifers) and multiparous (second or greater lactation/parity) Holstein cows were assigned to each treatment group at each location. Tables 1 through 4 summarize the doses of sometribove and number of cows starting treatment in each study.

Table 1. Number of Cows Starting Treatment in the **Intramuscular Dose Response Study (IM-Dose)**.

| Location and Study # | Parity[a] | Sometribove Dose (mg every 14 d) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | Total |
| Missouri 86-023 | P | 7 | 7 | 7 | 7 | 28 |
| | M | 14 | 15 | 14 | 14 | 57 |

[a]P = Primiparous; M = Multiparous

Table 2. Number of Cows Starting Treatment in the **Multi-location Intramuscular Single Dose Study (IM-Single)**.

| Location and Study # | Parity[a] | Sometribove Dose (mg every 14 d) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | | 500 | | Total |
| Arizona 85-039 | P | 9 | | 9 | | 18 |
| | M | 32 | | 31 | | 63 |
| New York 85-038 | P | 12 | | 12 | | 24 |
| | M | 30 | | 30 | | 60 |
| Missouri 85-021 | P | 13 | | 13 | | 26 |
| | M | 50 | | 50 | | 100 |
| Utah 86-003 | P | 12 | | 12 | | 24 |
| | M | 24 | | 25 | | 49 |
| Total | P | 46 | | 46 | | 92 |
| | M | 136 | | 136 | | 272 |

[a]P = Primiparous; M = Multiparous

Table 3. Number of Cows Starting Treatment in the **Intramuscular Versus Subcutaneous Route of Injection Study (IM/SC Bridging)**.

| Location and Study # | Parity[a] | Sometribove Dose (mg every 14 d) | | | | |
|---|---|---|---|---|---|---|
| | | 0 - IM | 0 - SC | 500 - IM | 500 - SC | Total |
| Missouri 86-032 | P | 3 | 4 | 7 | 7 | 21 |
| | M | 8 | 7 | 14 | 14 | 43 |

[a]P = Primiparous; M = Multiparous

Table 4. Number of Cows Starting Treatment in the **Multi-location Subcutaneous Dose Response Study (SC-Dose)**.

| Location and Study # | Parity[a] | Sometribove Dose (mg every 14 d) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | Total |
| Arizona 87-023 | P | 4 | 4 | 5 | 4 | 17 |
| | M | 12 | 12 | 10 | 12 | 46 |
| New York 87-034 | P | 6 | 6 | 5 | 6 | 23 |
| | M | 6 | 7 | 6 | 6 | 25 |
| Florida 87-029 | P | 9 | 9 | 10 | 9 | 37 |
| | M | 8 | 8 | 9 | 9 | 34 |
| Utah 87-024 | P | 8 | 8 | 8 | 8 | 32 |
| | M | 10 | 10 | 9 | 11 | 40 |
| Total | P | 27 | 27 | 28 | 27 | 109 |
| | M | 36 | 37 | 34 | 38 | 145 |

[a]P = Primiparous; M = Multiparous

Detailed descriptions of these studies are provided in the FOI Summary dated November 5, 1993 (see Sections 5.a, 6.c, 6.d, and 6.e). Briefly, sometribove treatment started during the 9$^{th}$ week after calving (60 ± 3 days in milk [DIM]) and continued until cows were dried off or removed from the study. Cows were monitored from the calving before the start of treatment through the subsequent calving (SC-Dose and IM/SC Bridging Studies), 3 weeks after the subsequent calving (IM-Dose), or 8 weeks after subsequent calving (IM-Single). During lactation, cows were milked twice a day at each study location. During the pretreatment and treatment periods, milk from each quarter of each study cow was examined at every milking for signs of clinical mastitis. Each cow was observed daily for health abnormalities by study personnel during pretreatment, treatment, and the dry period at all studies, and through 3 or 8 weeks of the subsequent lactation for the IM-Dose and IM-Single Studies, respectively. All therapeutic treatments administered to study animals were recorded. In addition, a physical examination of each cow was performed by a veterinarian during pretreatment (40 DIM) and at the end of treatment at all studies, at mid-treatment (180 DIM) at the IM-Dose, IM/SC Bridging, and IM-Single Studies, and early in the subsequent lactation at the IM-Dose and IM-Single Studies. Evaluation of the effects of sometribove on reproduction in these studies is discussed in Section 6.i and 6.l of the FOI Summary dated November 5, 1993, and in Section 3.e, 3.f, and 3.g, below. Calves born to study cows after the lactation of treatment were weighed at birth.

Post-Approval Monitoring Program Study (PAMP Study)

Following approval of the original NADA, a 28-Herd One-Lactation Post-Approval Monitoring Program Study (PAMP Study) was conducted on commercial dairy farms in the U.S. to evaluate the effectiveness and target animal safety of sometribove under actual conditions of use (see FOI Summary dated December 27, 2001, Section 4.b). Table 5 summarizes the study locations and number of cows starting treatment at each location.

Table 5. Number of Cows Starting Treatment in the **28-Herd One-Lactation Post-Approval Monitoring Program Study (PAMP Study)**.

| Herd ID | State | # Cows Starting Treatment | Times Milked per Day |
|---|---|---|---|
| **Midwest** | | | |
| MA | MN | 38 | 3 |
| MB | MN | 22 | 3 |
| MC | WI | 20 | 2 |
| MD | WI | 52 | 3 |
| ME | WI | 54 | 3 |
| MF | WI | 53 | 3 |
| MG | WI | 47 | 2 |
| **Northeast** | | | |
| NA | NJ | 53 | 2 |
| NB | NJ | 56 | 3 |
| NC | PA | 52 | 2 |
| ND | NY | 48 | 2 |
| NE | NY | 54 | 3 |
| NF | NY | 52 | 3 |
| NG | PA | 12 | 2 |
| NH | PA | 14 | 2 |
| **Southeast** | | | |
| SA | SC | 18 | 2 |
| SB | FL | 50 | 3 |
| SC | SC | 49 | 2 |
| SD | SC | 56 | 2 |
| SE | FL | 48 | 4 |
| SF | FL | 41 | 2 |
| **West** | | | |
| WA | ID | 67 | 3 |
| WB | CO | 49 | 3 |
| WC | CO | 48 | 3 |
| WD | CO | 48 | 3 |
| WE | ID | 15 | 2 |
| WF | CA | 49 | 2 |
| WG | CA | 48 | 2 |
| **Total = 28 herds** | | **1213 cows started treatment** | |

Holstein cows were used at all locations except for herds "SC" and "WE," which used Jersey cows. Of the 1213 cows starting treatment in the PAMP Study (Table 5), 85 were excluded from data analyses 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 of the PAMP Study.

| | Dose of Sometribove (mg every 14 days) | | |
|---|---|---|---|
| Parity | 0 | 500 | Totals |
| Primiparous | 209 | 210 | 419 |
| Multiparous | 356 | 353 | 709 |
| Totals | 565 | 563 | 1128 |

Detailed descriptions of the PAMP Study are provided in the FOI Summary dated December 27, 2001, Section 4.b. Briefly, sometribove treatment started between 57 and 70 DIM and continued for one lactation until cows were dried off or removed from the study. Pregnant cows were monitored through calving. Incidence of clinical mastitis was recorded during lactation. Each cow was observed daily for health abnormalities by herd personnel from the calving before start of treatment through dry-off or removal from treatment. All therapeutic treatments administered to study animals were recorded. In addition, the herd veterinarian observed all study cows every 14 days during lactation and recorded any clinical observations. Reproduction records were maintained according to each herd's practice. Calves born to study cows were not weighed.

**b. Clinical Mastitis**

The statements pertaining to clinical mastitis on the original product labeling for sometribove were as follows:

> "Cows injected with POSILAC are at an increased risk for clinical mastitis (visibly abnormal milk). The number of cows affected with clinical mastitis and the number of cases per cow may increase." (See FOI Summary dated November 5, 1993, Section 6.j.)

The effects of sometribove treatment on the incidence of clinical mastitis was reevaluated using three datasets:

First dataset: Original NADA Studies: Pooled IM-Dose, IM-Single*, IM/SC Bridging, and SC-Dose* Studies

Second dataset: PAMP Study

Third dataset: SC Studies: Pooled IM/SC Bridging (SC injected cows only), SC-Dose*, and PAMP Studies

*excluding Utah locations.

Milk from each quarter of each study cow was examined for signs of clinical mastitis at every milking from the calving before start of treatment through dry-off or removal from study. Clinical mastitis was defined as the presence of abnormal milk, e.g., flakes, clots, watery secretions, or discoloration from blood

or serum. Therapeutic treatment of clinical mastitis was per standard operating procedure at each specific location and typically included antibiotic infusion into the affected quarter. However, clinical mastitis was not usually treated at the Utah locations for the IM-Single and SC-Dose Studies (see FOI Summary dated November 5, 1993, Sections 5.a and 6.e). The lack of therapeutic treatment of clinical mastitis was not consistent with accepted U.S. mastitis management practices. Therefore, cows at the Utah locations for the IM-Single and SC-Dose studies were excluded from analysis of clinical mastitis data.

Incidence of clinical mastitis in the original NADA studies was evaluated during the treatment period using all cows starting treatment. (One primiparous and 2 multiparous cows had been excluded from the analysis for the original NADA.) For the PAMP study, incidence of clinical mastitis during the treatment period was evaluated using the number of cows indicated in Table 6 for each treatment-parity group.

Variables

The following four variables were analyzed:

Number of "cows affected" with clinical mastitis was defined as the number of cows in a treatment-parity group that had at least one "case" of clinical mastitis (see next definition) during the treatment period per number of cows starting treatment in that treatment-parity group.

"Cases" of clinical mastitis were the number of clinical mastitis cases per quarter per cow day when a new case could be observed. A "case" of clinical mastitis was defined as at least one observation of abnormal milk. The end of a clinical case was defined as the last milking with abnormal milk followed by at least 21 consecutive days of normal milk in that quarter. Return to abnormal milk in the affected quarter in less than 21 days was considered the same clinical mastitis case unless a different organism was cultured from the affected quarter. If a different organism was cultured, that constituted a new mastitis case.

"Days affected" with clinical mastitis was defined as the number of days affected with clinical mastitis per cow days observed. Cases in more than one quarter in the same cow on a given day were consolidated.

"Average duration" of clinical cases of mastitis was calculated as the average length of all cases of mastitis for each cow. (For the original NADA, "total duration" of clinical cases of mastitis was evaluated, which was the sum of lengths of all cases of mastitis for each cow.)

Methods of Analyses

Generalized linear mixed model methods (GLIMMIX macro in SAS) were used to analyze the clinical mastitis variables "cows affected," "cases," and "days affected." "Cows affected" was analyzed using a binomial error distribution and a logit link function. "Cases" and "days affected" were analyzed using Poisson error distributions and log link functions, with the log of the days at risk as offsets. For all three variables, the extra-dispersion parameter was allowed to vary, in order to accommodate possible over-dispersion. Mixed model methods (MIXED procedure in SAS) were used to analyze the clinical mastitis variable "average duration." Separate analyses were done for each parity group (primiparous and multiparous). Sometribove level was the only fixed effect in the models. Random effects in the model included location and the interaction of sometribove level by location. A single degree of freedom linear contrast on sometribove levels and a two degree of freedom contrast for deviation from linearity also were tested in these analyses. Best linear unbiased estimates (BLUE) of means and standard errors on the original scale were reported for those variables analyzed using MIXED and GLIMMIX methodology.

Effects were tested at the 10% level of significance. Biological interpretations of significant results considered overall incidence rate and consistency among treatment dose groups and studies.

RESULTS

In the reanalyzed data from the original NADA studies, sometribove treatment had a significant linear effect on "cows affected" with clinical mastitis for primiparous cows, and 21.51% of primiparous cows treated with 500 mg sometribove had clinical mastitis compared to 11.82% of controls (Table 7; probabilities for significant results [P≤.10] are shown in **bold**). "Cases," "days affected," and "average duration" were not significantly affected by sometribove treatment in primiparous cows (Table 7). In multiparous cows, sometribove treatment was associated with significantly more "cases" of clinical mastitis (Table 8). The case rate per 100 cow days at risk for multiparous cows treated with 500 mg sometribove was 0.26 compared to 0.14 for controls (Table 8). No other variables were affected in multiparous cows (Table 8).

Table 7. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Primiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies).

| Variable | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Primiparous Cows** | | | | | | | |
| N | 67 | 26 | 75 | 26 | | | |
| Total Cow Days | 16449 | 7487 | 19330 | 7928 | | | |
| Cows Affected (%)[d] | 11.82 | 23.40 | 21.51 | 35.24 | 0.158 | **0.037** | 0.643 |
| Cases/100 Cow Days Risk[d] | 0.08 | 0.13 | 0.16 | 0.18 | 0.507 | 0.183 | 0.905 |
| Days Affected/100 Cow Days Risk[d] | 0.32 | 0.76 | 0.49 | 0.36 | 0.466 | 0.957 | 0.304 |
| Avg Case Duration (days)[e] | 5.44 | 8.39 | 5.57 | 2.63 | 0.114 | 0.125 | 0.151 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[e] Mixed Model Analysis; results are reported as least-squares means.

Table 8. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies).

| Variable | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Multiparous Cows** | | | | | | | |
| N | 167 | 42 | 178 | 41 | | | |
| Total Cow Days | 38936 | 10341 | 43837 | 10314 | | | |
| Cows Affected (%)[d] | 19.43 | 18.93 | 32.58 | 24.30 | 0.103 | 0.265 | 0.238 |
| Cases/100 Cow Days Risk[d] | 0.14 | 0.14 | 0.26 | 0.13 | **0.085** | 0.811 | 0.117 |
| Days Affected/100 Cow Days Risk[d] | 0.56 | 0.60 | 1.02 | 0.61 | 0.157 | 0.593 | 0.257 |
| Avg Case Duration (days)[e] | 5.19 | 5.82 | 5.50 | 7.81 | 0.540 | 0.209 | 0.538 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[e] Mixed Model Analysis; results are reported as least-squares means.

In the PAMP study, sometribove treatment had no significant effects on the incidence of clinical mastitis in primiparous cows (Table 9). For multiparous cows, "cows affected" was significantly greater in the sometribove-treated cows compared to controls (28.71 vs. 22.51%; Table 10). "Cases," "days affected," and "average duration" were not affected by sometribove treatment in multiparous cows (Table 10).

Table 9. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Primiparous Cows in PAMP Study.

| Variable | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|
| | 0 | 500 | |
| **Primiparous Cows** | | | |
| N | 209 | 210 | |
| Total Cow Days | 53961 | 55704 | |
| Cows Affected (%)[b] | 14.71 | 18.48 | 0.370 |
| Cases/100 Cow Days Risk[b] | 0.10 | 0.12 | 0.392 |
| Days Affected/100 Cow Days Risk[b] | 0.28 | 0.32 | 0.609 |
| Avg Case Duration (days)[c] | 4.82 | 4.44 | 0.635 |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[c] Mixed Model Analysis; results are reported as least-squares means.

Table 10. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Multiparous Cows in PAMP Study.

| Variable | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|
| | 0 | 500 | |
| **Multiparous Cows** | | | |
| N | 356 | 353 | |
| Total Cow Days | 87075 | 88590 | |
| Cows Affected (%)[b] | 22.51 | 28.71 | **0.064** |
| Cases/100 Cow Days Risk[b] | 0.16 | 0.21 | 0.169 |
| Days Affected/100 Cow Days Risk[b] | 0.56 | 0.67 | 0.381 |
| Avg Case Duration (days)[c] | 5.79 | 5.94 | 0.860 |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[c] Mixed Model Analysis; results are reported as least-squares means.

In the third dataset, where data from subcutaneously-injected cows in the original NADA studies were pooled with those from cows in the PAMP Study, trends for more sometribove-treated cows to have clinical mastitis than controls were no longer significant in primiparous cows (Table 11). "Average duration" of clinical mastitis cases was significantly decreased by sometribove treatment, and treatment had a linear effect (Table 11). However, this appeared to be an incidental result reflected in a significant deviation from linearity, and average duration between primiparous cows treated with 500 mg sometribove versus controls was similar (Table 11). In multiparous cows, sometribove treatment had a significant effect on "cows affected" with clinical mastitis, and 28.86% of multiparous cows in the 500 mg treatment group had clinical mastitis during treatment compared to 22.50% of controls (Table 12).

Table 11. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Primiparous Cows in SC Studies (Pooled SC-Dose, PAMP, and [SC injected cows of ] IM/SC Bridging Studies).

| Variable | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Primiparous Cows** | | | | | | | |
| N | 232 | 19 | 237 | 19 | | | |
| Total Cow Days | 59763 | 5458 | 62892 | 5753 | | | |
| Cows Affected (%)[d] | 13.87 | 16.81 | 17.97 | 26.91 | 0.560 | 0.236 | 0.884 |
| Cases/100 Cow Days Risk[d] | 0.09 | 0.12 | 0.11 | 0.18 | 0.510 | 0.212 | 0.804 |
| Days Affected/100 Cow Days Risk[d] | 0.26 | 0.60 | 0.31 | 0.30 | 0.455 | 0.911 | 0.328 |
| Avg Case Duration (days)[e] | 4.78 | 10.00 | 4.51 | 2.55 | **0.062** | **0.038** | **0.038** |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[e] Mixed Model Analysis; results are reported as least-squares means.

Table 12. Effect of Sometribove Treatment on Incidence of Clinical Mastitis in Multiparous Cows in SC Studies (Pooled SC-Dose, PAMP, and [SC injected cows of ] IM/SC Bridging Studies).

| Variable | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Multiparous Cows** | | | | | | | |
| N | 389 | 27 | 392 | 27 | | | |
| Total Cow Days | 95195 | 6914 | 98459 | 7057 | | | |
| Cows Affected (%)[d] | 22.50 | 10.45 | 28.86 | 24.99 | **0.084** | 0.286 | 0.237 |
| Cases/100 Cow Days Risk[d] | 0.16 | 0.06 | 0.21 | 0.13 | 0.262 | 0.794 | 0.380 |
| Days Affected/100 Cow Days Risk[d] | 0.54 | 0.27 | 0.69 | 0.62 | 0.428 | 0.470 | 0.582 |
| Avg Case Duration (days)[e] | 5.49 | 7.63 | 5.89 | 10.05 | 0.356 | 0.150 | 0.304 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis; results are reported as least-squares means.
[e] Mixed Model Analysis; results are reported as least-squares means.

## CONCLUSIONS

The risk of clinical mastitis associated with sometribove treatment was not as great as observed for the original NADA approval (see FOI Summary dated November 5, 1993, Section 6.j). Nevertheless, cows treated with 500 mg sometribove every 14 days, even by the approved subcutaneous injection route, are more likely to have mastitis than non-treated cows.

Product labeling statements were revised as follows to reflect results of the new analyses:

> "Cows treated with POSILAC are at an increased risk for mastitis (visibly abnormal milk)."

Labeling still advises users of the product to have comprehensive mastitis management practices in place before using POSILAC.

**c. Subclinical Mastitis**

The original product labeling for sometribove stated the following regarding effects on subclinical mastitis:

> "In addition, the risk of subclinical mastitis (milk not visibly abnormal) is increased. In some herds, use of POSILAC has been associated with increases in somatic cell counts." (See FOI Summary dated November 5, 1993, Section 6.j.)

The statement associated specifically with subclinical mastitis was based on results of periodic bacterial culturing of milk from cows in the original NADA studies for sometribove (see FOI Summary dated November 5, 1993, Section 6.j).

Milk somatic cell count accurately reflects the incidence of subclinical mastitis in dairy cows. Thus, stating on product labeling that the risks of both subclinical mastitis and higher milk somatic cell count are increased in sometribove-treated cows is redundant. Increased milk somatic cell count is a more meaningful and practical expression of this risk to commercial U.S. dairy producers. Thus, the reference to increased subclinical mastitis was removed from the labeling of POSILAC, and the increased risk of higher milk somatic cell count was combined with the statement pertaining to clinical mastitis as follows:

> "Cows treated with POSILAC are at an increased risk for mastitis (visibly abnormal milk) and may have higher milk somatic cell counts."

**d. Cow Health**

The effects of sometribove treatment on cow health were reevaluated using two datasets:

First dataset: Original NADA Studies: Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies

Second dataset: PAMP Study

In each study, all cows were observed daily by study personnel for health abnormalities. Also, in the PAMP Study and in some of the original NADA studies, clinical observations of all study cows were recorded during periodic physical examinations by a veterinarian. Thus, within each of the two datasets, separate analyses were conducted on daily health observations and periodic veterinary observations. Incidence of therapeutic treatment of study cows was also analyzed for each dataset.

As described for the original NADA (see FOI Summary dated November 5, 1993, Section 6.k), all animal health and therapy data were grouped within the following major biological systems or categories:

Circulatory/Lymphatics
Digestive
Genito-Urinary
Musculoskeletal
Metabolic
Respiratory
Udder
Eye and Conjunctiva
Integumentary
Therapy
Miscellaneous

The data were further grouped into subsystem within system, and signs and diagnoses within subsystem. The data were then analyzed at each of these levels. The subsystems and signs/diagnoses to which health observations were further categorized were dependent on the data recorded in each study, and consequently, were different for each of the two major datasets.

Original NADA Studies

Cows in the original NADA studies were monitored from the calving before start of treatment through the dry period following the lactation of treatment for all studies, and during part of the early subsequent lactation for two studies (IM-Dose and IM-Single Studies).

Daily health observation data were analyzed in each of the following study periods:

**Pre**: calving to start of treatment (cows untreated);
**Std Trtmt**: standardized treatment period (start of treatment to 252 days of treatment [18 injection cycles], dry-off, or removal, whichever came first);
**Full Trtmt**: full treatment period (start of treatment to dry-off or removal, whichever came first);
**Dry**: dry period following the lactation of treatment (cows untreated);
**Next**: up to 56 days of the subsequent lactation (IM-Dose and IM-Single Studies; cows untreated).

All cows starting a study period for the original NADA studies were included in the analysis of daily cow health data for that period. Most effects of treatment were noted during the treatment period, and these results were usually presented for the "full treatment period."

Veterinary clinical observation data obtained from physical examinations conducted at the following study time-points during the original NADA studies were also analyzed:

**40 dim**: pretreatment physical examination at 40 DIM (all studies; cows untreated);
**180 dim**: physical examination at 180 DIM (IM/SC Bridging, IM-Dose, and IM-Single Studies);
**end trtmt**: physical examination during last treatment cycle (all studies);
**next**: physical examination during early subsequent lactation (IM-Dose and IM-Single Studies; cows untreated).

All cows in the original NADA studies given physical examinations at these time points were included in the analysis of veterinary physical examination data.

PAMP Study

Cows in the PAMP Study were monitored for health abnormalities from the calving before start of treatment through dry-off or removal from treatment.

Daily health observation data were analyzed for each of the following study periods:

**Pre**: calving to start of treatment (cows untreated);
**Trtmt**: treatment period (start of treatment to dry-off or removal, whichever came first).

Table 6 lists the number of cows included in analysis for each treatment-parity group during these study periods.

Physical examinations of cows in the PAMP Study were performed by a veterinarian every 14 days beginning at the start of treatment. These data were analyzed during the following study periods:

**pre**: one examination at start of treatment (cows untreated);
**trtmt**: examinations during treatment period (start of treatment to dry-off or removal, whichever came first).

Cows listed in Table 6 that were given physical examinations during these study periods were included in the analysis of veterinary clinical data for the PAMP Study.

Variables

For daily health observation data, the following two variables were analyzed for the original NADA studies and the PAMP Study:

Number of "cows affected" was defined as the number of cows in a treatment-parity group that had a health observation at least once during a study period per number of cows starting that study period in that treatment-parity group.

"Days affected" was defined as the number of days affected with a health problem for a treatment-parity group during a study period per cow days at risk during that study period for the treatment-parity group.

For veterinary clinical observation data obtained from the original NADA studies, only "cows affected" was analyzed. Both "cows affected" and "days affected" were analyzed for veterinary clinical data from the PAMP Study.

Methods of Analyses

The variables "cows affected" and "days affected" were analyzed using the methods described in detail under Section 3.b.

If the GLIMMIX macro did not converge after 50 iterations or the convergence criterion was greater than 0.5 after 20 iterations, then a polynomial model was fit using the GLIMMIX macro. Three fixed effect continuous variables were defined: the linear, quadratic and cubic effects associated with the four sometribove dose levels. Random effects included location and location by linear, location by quadratic, and location by cubic interactions. To test for deviation from linearity in the polynomial model, the difference in scaled deviance between the full cubic model and a reduced model that included only the linear effect was calculated. The probability of the linear effect in the tables is the probability associated with

the linear effect in the full cubic model. Random terms were identical in the full and reduced models. The difference in scaled deviance is distributed as a two degree of freedom Chi-squared variate. If either of the polynomial models did not converge using the same criteria and procedures as for the standard parameterization or if the quadratic or cubic fixed effects had zero degrees of freedom for testing in the full cubic model, then the data were transformed and analyzed using the MIXED procedure. "Cows affected" was transformed using a logit transformation, while "days affected" was transformed using log (days affected/days at risk). In both cases, a continuity correction of 0.5 was used to avoid problems with logarithms of zero. The transformed values were calculated from sometribove by location cell totals.

For variables observed only at a single location, data were analyzed as generalized linear models using the GENMOD procedure in SAS. The only independent variable in these models was sometribove level. When more than two levels of sometribove were observed, linear contrasts and deviation from linearity contrasts were calculated.

Sparseness Criteria: Variables for which there were five or more observations in any sometribove treatment by location cell within parity group were analyzed using parametric methods described in the previous paragraphs. Variables for which there were two or fewer observations in all sometribove treatment by location cells were summarized and tabulated but were not statistically analyzed. If there were three or four observations in any single sometribove treatment by location cell, exact methods were used for analysis. The exact analog of the Cochran-Armitage trend test was selected to test for sometribove dose dependency, with location as a stratifying variable (Mehta and Patel, 1996). The estimate of the slope in these tests models the probability of no event occurring. For the two-dose PAMP dataset, this analysis is equivalent to a stratified Fisher's Exact Test. Tests for deviations from linearity were not done when exact methods were used.

Effects were tested at the 10% level of significance. Biological interpretations of significant results considered overall incidence rate and consistency among treatment dose groups and studies.

## RESULTS

As with the original NADA (see FOI Summary dated November 5, 1993, Section 6.k), there continued to be no negative effects associated with sometribove treatment for the Circulatory/Lymphatics, Metabolic, Respiratory, Eye and Conjunctiva, and Integumentary Systems.

Label cautions associated with the effects of sometribove treatment on the Digestive and Genito-Urinary Systems were removed, and cautions associated with the Musculoskeletal System were modified (see below). Precautions regarding the Udder System, frequency of use of medication, and increased body temperature in sometribove-treated cows remained on product labeling (see below).

Unless otherwise indicated, significant effects of treatment are reported from the daily health observation data.

Digestive System

The original product labeling for sometribove stated:

> "Use of POSILAC may result in an increase in digestive disorders such as indigestion, bloat, and diarrhea. There may be an increase in the number of cows experiencing periods of 'off-feed' (reduced feed intake) during use of POSILAC." (See FOI Summary dated November 5, 1993, Section 6.k.)

Digestive Disorders. Reanalysis of daily health observation data from the original NADA studies indicated that, in primiparous cows during the full treatment period, sometribove treatment was associated with significant linear increases in "cows affected" and "days affected" with abnormalities in rumen motility and "days affected" with bloat. These effects were observed at only the 500 and 750 mg doses (Table 13). Incidence of rumen motility abnormalities was greater for the 500 mg dose group than the 750 mg group (Table 13). The incidences of rumen motility abnormalities and bloat were not significantly affected in multiparous cows treated with sometribove in the original NADA studies. In the PAMP Study, these abnormalities were not significantly increased in sometribove-treated cows of either parity group.

Table 13. Effect of Sometribove Treatment on Incidence of Rumen Abnormalities in Primiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Rumen Motility – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%)[d] | | 1.15 | 0 | 9.47 | 2.94 | | **0.057** | |
| Days Affected/100 Cow Days Risk[d] | | 0.0045 | 0 | 0.0438 | 0.0101 | | **0.043** | |
| **Bloat – Primiparous Cows** | | | | | | | | |
| Cows Affected (%) | **Full Trtmt** | 0 | 0 | 4.21 | 5.88 | NA[e] | NA | NA |
| Days Affected/100 Cow Days Risk[d] | | 0 | 0 | 0.0358 | 0.0303 | | **0.006** | |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Exact Trend Test.
[e] NA = No analysis necessary (<3 observations in each cell).

Sometribove treatment was associated with a significant effect on "days affected" with diarrhea in multiparous cows in the original NADA studies (Table 14). The effect deviated from linearity, and only the 500 mg sometribove group had greater "days affected" than controls (Table 14). The effect of treatment on "cows affected" with diarrhea for multiparous cows in the original NADA studies also deviated from linearity (Table 14). Percent "cows affected" tended to be similar between the 500 mg dose group and controls, but was lower in the 250 and 750 mg groups (Table 14). There was no significant effect of sometribove treatment on the incidence of diarrhea in primiparous cows in the original NADA studies, and there was no significant effect in either parity group in the PAMP Study.

Table 14. Effect of Sometribove Treatment on Incidence of Diarrhea in Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Diarrhea – Multiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 201 | 52 | 212 | 52 | | | |
| Cows Affected (%)[d] | | 29.35 | 3.85 | 28.30 | 5.77 | **0.058** | 0.275 | **0.047** |
| Days Affected/100 Cow Days Risk[d] | | 0.1910 | 0.0152 | 0.2512 | 0.0298 | **0.004** | 0.581 | **0.003** |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

There was no significant effect of sometribove treatment on incidence of indigestion in the original NADA studies. In the PAMP Study, multiparous cows in the sometribove treatment group had significantly more "days affected" with indigestion (Table 15). There was no significant effect of treatment in primiparous cows in the PAMP Study.

Table 15. Effect of Sometribove Treatment on Incidence of Indigestion in Multiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Indigestion – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%)[b] | | 0.84 | 2.27 | 0.134 |
| Days Affected/100 Cow Days Risk[b] | | 0.0046 | 0.0147 | **0.050** |

[a] Probability A is for treatment main effects.
[b] Exact Trend Test.

Off-feed. As with the original NADA, incidence of "off-feed" was determined by two methods for the clinical studies from the original NADA. The first method was based on recorded observations by study personnel of a cow eating less than normal, e.g., the person's perception that the cow appeared to not be eating, had a large feed refusal, etc. In the second method, incidence of daily high feed refusal was calculated on an individual cow basis using the cow's feed offered and refused data. If a cow had a daily feed refusal that weighed ≥50% of the cow's average daily feed intake for the previous seven days, the cow was recorded as having a high feed refusal that day.

Only the first method of recording the incidence of off-feed (i.e., perception) was used for the PAMP Study because feed intake data were not measured.

"Days affected" in which cows were perceived to be off-feed was significantly increased in primiparous cows treated with sometribove compared to controls in the original NADA studies (Table 16). The effect deviated from linearity (Table 16). There was no significant effect of sometribove treatment on this variable in multiparous cows in the original NADA studies.

Table 16. Effect of Sometribove Treatment on Incidence of "Off-Feed" based on Perception in Primiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Perceived Off-Feed – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%)[d] | | 5.75 | 29.41 | 21.05 | 14.71 | | 0.118 | |
| Days Affected/100 Cow Days Risk[e] | | 0.0405 | 0.1516 | 0.1472 | 0.0908 | **0.041** | 0.306 | **0.035** |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Exact Trend Test.
[e] Generalized Linear Mixed Model Analysis.

In the PAMP Study, primiparous and multiparous cows treated with sometribove had significantly more "days affected" in which they were perceived to be off-feed, and sometribove-treated multiparous cows had significantly more "cows affected" (Table 17). However, the results were observed in less than 3% of sometribove-treated cows and for very few days.

Table 17. Effect of Sometribove Treatment on Incidence of "Off-Feed" based on Perception in Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Perceived Off-Feed – Primiparous Cows** | | | | |
| N | **Trtmt** | 209 | 210 | |
| Cows Affected (%) | | 0.96 | 2.86 | NA[b] |
| Days Affected/100 Cow Days Risk[c] | | 0.0074 | 0.0359 | **0.066** |
| **Perceived Off-Feed – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%)[d] | | 0.28 | 2.83 | **0.004** |
| Days Affected/100 Cow Days Risk[c] | | 0.0012 | 0.0248 | **0.042** |

[a] Probability A is for treatment main effects.
[b] NA = No analysis necessary (<3 observations in each cell).
[c] Generalized Linear Mixed Model Analysis.
[d] Exact Trend Test.

When incidence of off-feed was calculated for cows in the original NADA studies, sometribove treatment was associated with significantly fewer "cows affected" and "days affected" in primiparous cows (Table 18). There was no significant effect of sometribove treatment in multiparous cows (Table 18).

Table 18. Effect of Sometribove Treatment on Incidence of "Off-Feed" Calculated for Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Calculated Off-Feed – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%)[d] | | 47.13 | 29.41 | 36.84 | 44.12 | **0.088** | 0.507 | **0.070** |
| Days Affected/100 Cow Days Risk[d] | | 0.3646 | 0.2729 | 0.2825 | 0.3430 | **0.100** | 0.251 | 0.133 |
| **Calculated Off-Feed – Multiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 201 | 52 | 212 | 52 | | | |
| Cows Affected (%)[d] | | 36.32 | 51.92 | 38.21 | 53.85 | 0.302 | 0.205 | 0.287 |
| Days Affected/100 Cow Days Risk[d] | | 0.2679 | 0.4564 | 0.3225 | 0.4174 | 0.155 | 0.214 | 0.226 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

CONCLUSIONS (Digestive System)

The evaluation of the effects of sometribove treatment on cow health for the original NADA included results from a Multi-lactation Chronic Animal Toxicity Study with doses up to 6 times the intended dose of 500 mg every 14 days (see FOI Summary dated November 5, 1993, Section 6.b). Results of that study contributed to the decision to state on product labeling that sometribove treatment may increase digestive disorders, such as indigestion, bloat, and diarrhea, in treated cows (see FOI Summary dated November 5, 1993, Section 6.k). The original NADA clinical studies and the PAMP Study used doses similar to the intended dose. The current reanalysis of cow health data from these studies indicated that effects of sometribove treatment on the incidence of indigestion, bloat, and diarrhea were not consistent across studies, parity groups, and/or sometribove doses. Based on these results, the statement on product labeling indicating that sometribove treatment may result in increased digestive disorders such as indigestion, bloat, and diarrhea was removed.

Sometribove-treated cows were perceived to be off-feed more often than control cows. However, in the original NADA studies, this was observed only in primiparous cows. In the PAMP Study, the effect was observed for a very small number of cows and days. When feed refusals were actually measured and compared to a cow's feed intake during the previous week, sometribove-treated cows in the original NADA studies did not have a greater incidence of being off-feed. Sometribove-treated cows produce more milk than untreated cows and would typically be offered more feed to support their increased milk production. As noted in the original NADA and on product labeling, sometribove-treated cows also eat more feed after being on treatment for several weeks (see FOI Summary dated November 5, 1993, Section 6.h). These effects may have contributed to the perception that sometribove-treated cows had more days of being off-feed; they were probably offered more feed, which could result in larger feed refusals despite having eaten more than control cows. The statement on product labeling stating that cows experience more periods of off-feed during treatment with sometribove was removed.

Genito-Urinary System

The original product labeling for sometribove stated:

> "Use of POSILAC has also been associated with increases in … disorders of the uterus during the treatment period. …Also, the incidence of retained placenta may be higher following subsequent calving." (See FOI Summary dated November 5, 1993, Section 6.k.)

Review of cow health data from the PAMP Study in 1997 indicated that incidence of disorders of the uterus was not significantly higher in cows treated with 500 mg sometribove every 14 days. Thus, this statement was removed from product labeling. Also, the statement regarding the increased incidence of retained placenta was modified to remove the phrase "following subsequent calving." Thus, the labeling for sometribove with respect to the Genito-Urinary System was modified to the following:

> "…Also, the incidence of retained placenta may be higher." (See FOI Summary dated December 27, 2001, Section 4.b.)

Disorders of the Uterus. The reanalysis of the genito-urinary data from the original NADA studies and PAMP Study did not alter the conclusion reached in 1997. The incidence of disorders of the uterus was not significantly increased in cows of either parity group treated with sometribove.

Retained Placenta. In the early subsequent lactation period ("next") for the original NADA studies, "days affected" with retained placenta was significantly increased in multiparous cows that had been treated with sometribove, although the effect decreased with dose and was higher than controls only in the 250 and 500 mg treatment groups (Table 19). "Cows affected" with retained placenta was not significantly affected by sometribove treatment (Table 19.) No significant effect of sometribove treatment on the incidence of retained placenta was observed for primiparous cows in the original NADA studies.

Table 19. Effect of Sometribove Treatment on Incidence of Retained Placenta in Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | **Study Period** | **Sometribove Dose (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Retained Placenta – Multiparous Cows** | | | | | | | | |
| N | **Next** | 126 | 11 | 109 | 9 | | | |
| Cows Affected (%)[d] | | 15.87 | 27.27 | 22.94 | 11.11 | 0.486 | 0.744 | 0.525 |
| Days Affected/100 Cow Days Risk[d] | | 0.7489 | 2.1390 | 1.2607 | 0.5988 | **0.050** | 0.662 | 0.125 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

In the PAMP Study, multiparous cows treated with sometribove had significantly more "days affected" with retained placenta during the treatment period, but this was based on 0 and 2 cows in the control and treatment group, respectively (Table 20). These observations were likely associated with abortions because health observations of cows on the PAMP study were not continued beyond the treatment period. No observations of retained placenta were reported for primiparous cows during the treatment period in the PAMP Study.

Table 20. Effect of Sometribove Treatment on Incidence of Retained Placenta in Multiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Retained Placenta – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%) | | 0 | 0.57 | NA[b] |
| Days Affected/100 Cow Days Risk[c] | | 0 | 0.0102 | **0.004** |

[a] Probability A is for treatment main effects.
[b] NA = no analysis necessary (<3 observations in each cell).
[c] Exact Trend Test.

CONCLUSIONS (Genito-Urinary System)

A caution regarding uterine disorders remains off of product labeling.

The effect of sometribove treatment on "days affected" with retained placenta was not consistent across parity groups or study periods. Retained placenta during mid-lactation is caused by spontaneous abortion of the fetus. The clinical progress of this type of retained placenta is not comparable to that occurring after a full-term birth. Therefore, "cows affected" is a more meaningful variable to evaluate. "Cows affected" with retained placenta was not significantly affected by sometribove treatment. Thus, the statement that sometribove treatment is associated with an increased incidence of retained placenta was removed from product labeling.

Effect of sometribove treatment on the incidence of cystic ovaries is discussed in Section 3.e.

Musculoskeletal System

The original product labeling for sometribove stated:

> "Studies indicated that cows injected with POSILAC had increased numbers of enlarged hocks and lesions (e.g., lacerations, enlargements, calluses) of the knee (carpal region), and second lactation or older cows had more disorders of the foot region. However, results of these studies did not indicate that use of POSILAC increased lameness." (See FOI Summary dated November 5, 1993, Section 6.k.)

Hocks. In the original NADA studies, sometribove treatment of primiparous cows was associated with a significant linear effect on "days affected" with abnormalities of the Hock Subsystem (Table 21). An increase compared to controls was only noted for the 500 mg dose group. These abnormalities were primarily associated with swellings or abscesses. For multiparous cows in the original NADA, a similar trend was observed for the Hock Subsystem (data not shown). Sometribove treatment had a significant linear effect on "cows affected" with hock swellings for multiparous cows (Table 22).

Table 21. Effect of Sometribove Treatment on Incidence of Abnormalities of the Hock Subsystem for Primiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | **Study Period** | **Sometribove Dose (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Hock Subsystem – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%) | | 2.30 | 0 | 6.32 | 5.88 | NA[d] | NA | NA |
| Days Affected/100 Cow Days Risk[e] | | 0.0315 | 0 | 0.1313 | 0.0202 | | **<0.001** | |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] NA = No analysis necessary (<3 observations in each cell).
[e] Exact Trend Test.

Table 22. Effect of Sometribove Treatment on Incidence of Swollen Hocks for Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | **Study Period** | **Sometribove Dose (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Swollen Hocks – Multiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 201 | 52 | 212 | 52 | | | |
| Cows Affected (%)[d] | | 1.99 | 1.92 | 8.02 | 7.69 | 0.293 | **0.084** | 0.889 |
| Days Affected/100 Cow Days Risk[e] | | 0.0291 | 0.0152 | 0.1537 | 0.0596 | 0.336 | 0.176 | 0.710 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.
[e] Mixed Model Analysis.

Veterinary clinical observations recorded during physical examinations conducted at mid and/or late treatment on cows in the original NADA studies also associated sometribove treatment with significantly more swollen hocks in both parity groups (Table 23). Observations were most prevalent for the 500 mg dose group probably because of the greater number of cows in that sometribove treatment group.

Table 23. Effect of Sometribove Treatment on Incidence of Swollen Hocks for Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Veterinary Physical Examinations).

| | Study Time | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Swollen Hocks – Primiparous Cows** | | | | | | | | |
| N | **180 dim** | 59 | 7 | 67 | 7 | | | |
| Cows Affected (%)[d] | | 1.69 | 0 | 8.96 | 0 | | **0.100** | |
| N | **end trtmt** | 86 | 34 | 93 | 33 | | | |
| Cows Affected (%)[d] | | 1.16 | 0 | 5.38 | 15.15 | | **<0.001** | |
| **Swollen Hocks – Multiparous Cows** | | | | | | | | |
| N | **180 dim** | 161 | 14 | 170 | 13 | | | |
| Cows Affected (%)[d] | | 3.11 | 0 | 8.24 | 0 | | **0.037** | |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Exact Trend Test.

Based on daily health observations, "days affected" with swollen hocks was significantly increased in multiparous cows treated with sometribove in the PAMP Study, although incidence was very low (Table 24). There was no significant effect of sometribove treatment on swollen hocks in primiparous cows in the PAMP Study based on daily health observations. In veterinary clinical observations recorded during the PAMP Study, there was a significant increase in "days affected" with swollen hocks in sometribove-treated multiparous cows compared to controls, and a similar trend for primiparous cows (Table 25).

Table 24. Effect of Sometribove Treatment on Incidence of Swollen Hocks in Multiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Swollen Hocks – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%) | | 0 | 0.85 | NA[b] |
| Days Affected/100 Cow Days Risk[c] | | 0 | 0.0079 | **0.015** |

[a] Probability A is for treatment main effects.
[b] NA = No analysis necessary (<3 observations in each cell).
[c] Exact Trend Test.

Table 25. Effect of Sometribove Treatment on Incidence of Swollen Hocks for Cows in PAMP Study (Veterinary Physical Examinations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Swollen Hocks – Primiparous Cows** | | | | |
| N | **trtmt** | 209 | 210 | |
| Cows Affected (%)[b] | | 2.39 | 6.67 | 0.337 |
| Days Affected/100 Cow Days Risk[b] | | 0.2440 | 1.8305 | 0.126 |
| **Swollen Hocks – Multiparous Cows** | | | | |
| N | **trtmt** | 354 | 353 | |
| Cows Affected (%)[b] | | 5.08 | 6.80 | 0.196 |
| Days Affected/100 Cow Days Risk[b] | | 0.5864 | 1.2492 | **<0.001** |

[a] Probability of treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

Knees (carpal region). There was no association between sometribove treatment and knee abnormalities in the daily health observations for either parity group of cows in the original NADA studies and the PAMP Study. Veterinary clinical observations at physical examinations conducted at mid and late treatment on multiparous cows in the original NADA studies revealed more abnormalities of the Knee/Carpus Subsystem in the sometribove treatment groups compared to controls (Table 26). Observations were predominantly due to calluses of the knee. This effect was not observed in primiparous cows in the original NADA studies.

Table 26. Effect of Sometribove Treatment on Incidence of Abnormalities of the Knee/Carpus Subsystem for Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Veterinary Physical Examinations).

| | Study Time | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Knee/Carpus Subsystem – Multiparous Cows** | | | | | | | | |
| N | **180 dim** | 161 | 14 | 170 | 13 | | | |
| Cows Affected (%)[d] | | 12.42 | 50.00 | 23.53 | 53.85 | **0.095** | **0.090** | 0.420 |
| N | **end trtmt** | 193 | 49 | 200 | 47 | | | |
| Cows Affected (%)[d] | | 4.66 | 6.12 | 12.50 | 8.51 | **0.048** | **0.029** | 0.725 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

Veterinary clinical observations recorded during physical examinations conducted throughout the PAMP Study revealed that primiparous cows treated with sometribove had more "days affected" with abnormalities of the Knee/Carpus Subsystem compared to controls, and these were associated with swellings of the knee (Table 27). However, these observations were recorded for very few primiparous cows (0 and 3 in the control and treatment groups, respectively), and this effect of sometribove treatment was not observed in multiparous cows in the PAMP Study.

Table 27. Effect of Sometribove Treatment on Incidence of Swollen Knees for Primiparous Cows in PAMP Study (Veterinary Physical Examinations).

| | **Study Period** | **Sometribove Dose (mg every 14 d)** | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Swollen Knees – Primiparous Cows** | | | | |
| N | **trtmt** | 209 | 210 | |
| Cows Affected (%) | | 0 | 1.43 | NA[b] |
| Days Affected/100 Cow Days Risk[c] | | 0 | 0.1569 | **0.030** |

[a] Probability A is for treatment main effects.
[b] NA = No analysis necessary (<3 observations in each cell).
[c] Exact Trend Test.

Foot/Hoof Region. In primiparous and multiparous cows in the original NADA studies, daily health observations revealed that sometribove treatment was associated with significantly more "days affected" with abnormalities of the Foot/Hoof Subsystem (Table 28). In primiparous cows, greater "days affected" than controls was observed only for the 500 mg dose group, and the effect in multiparous cows deviated from linearity (Table 28). These observations were associated with several different effects, such as swelling, infections, sores, and foot rot.

Table 28. Effect of Sometribove Treatment on Incidence of Abnormalities of the Foot/Hoof Subsystem for Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Foot/Hoof Subsystem – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%) | | 9.20 | 2.94 | 5.26 | 5.88 | NA[d] | NA | NA |
| Days Affected/100 Cow Days Risk[e] | | 0.0675 | 0.0303 | 0.0915 | 0.0504 | | **0.019** | 0.158 |
| **Foot/Hoof Subsystem – Multiparous Cows** | | | | | | | | |
| N | **Std Trtmt** | 201 | 52 | 212 | 52 | | | |
| Cows Affected (%)[f] | | 4.48 | 11.54 | 7.08 | 9.62 | | 0.359 | |
| Days Affected/100 Cow Days Risk[e] | | 0.0555 | 0.0939 | 0.0694 | 0.2467 | | 0.506 | **0.091** |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] NA = No analysis necessary (<3 observations in each cell).
[e] Generalized Linear Mixed Model Analysis (dose as a continuous variable).
[f] Exact Trend Test.

In the PAMP Study, "days affected" with abnormalities of the Foot/Hoof Subsystem was significantly increased in sometribove-treated cows compared to controls for both parity groups, and "cows affected" was significantly increased for multiparous cows treated with sometribove (Table 29). Veterinary clinical observations during the PAMP Study indicated that "cows affected" and "days affected" with abnormalities of the Foot/Hoof Subsystem were significantly increased in multiparous cows treated with sometribove compared to controls (Table 30). The effects again were associated with several abnormalities.

Table 29. Effect of Sometribove Treatment on Incidence of Abnormalities of the Foot/Hoof Subsystem in Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Foot/Hoof Subsystem – Primiparous Cows** | | | | |
| N | **Trtmt** | 209 | 210 | |
| Cows Affected (%)[b] | | 11.96 | 16.19 | 0.213 |
| Days Affected/100 Cow Days Risk[b] | | 0.0908 | 0.2100 | **0.039** |
| **Foot/Hoof Subsystem – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%)[b] | | 8.71 | 19.26 | **<0.001** |
| Days Affected/100 Cow Days Risk[b] | | 0.1344 | 0.2788 | **0.018** |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

Table 30. Effect of Sometribove Treatment on Incidence of Abnormalities of the Foot/Hoof Subsystem for Multiparous Cows in PAMP Study (Veterinary Physical Examinations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Foot/Hoof Subsystem – Multiparous Cows** | | | | |
| N | **trtmt** | 354 | 353 | |
| Cows Affected (%)[b] | | 9.04 | 13.88 | **0.024** |
| Days Affected/100 Cow Days Risk[b] | | 0.7539 | 1.8409 | **<0.001** |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

Lameness. There were no significant effects of sometribove treatment on the Gait Subsystem in the original NADA studies. In the PAMP Study daily observation dataset, multiparous cows treated with sometribove had significantly more "cows affected" with Gait Subsystem abnormalities than controls (see Table 31). These observations were primarily associated with lameness. Veterinary clinical observations from the PAMP Study also indicated significantly more "cows affected" as well as "days affected" with Gait Subsystem abnormalities for sometribove-treated multiparous cows compared to controls (Table 32). There was no significant effect of sometribove treatment on the Gait Subsystem in primiparous cows in the PAMP Study.

Table 31. Effect of Sometribove Treatment on Incidence of Abnormalities of the Gait Subsystem in Multiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Gait Subsystem – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%)[b] | | 6.74 | 11.61 | **0.037** |
| Days Affected/100 Cow Days Risk[b] | | 0.1413 | 0.0937 | 0.541 |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

Table 32. Effect of Sometribove Treatment on Incidence of Abnormalities of the Gait Subsystem for Multiparous Cows in PAMP Study (Veterinary Physical Examinations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Gait Subsystem – Multiparous Cows** | | | | |
| N | trtmt | 354 | 353 | |
| Cows Affected (%)[b] | | 20.34 | 25.50 | **0.054** |
| Days Affected/100 Cow Days Risk[b] | | 2.9988 | 4.6680 | **0.004** |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

CONCLUSIONS (Musculoskeletal System)

The product labeling for sometribove continues to state that treated cows tend to have more enlarged hocks.

No significant effects of sometribove treatment on the Knee/Carpus Subsystem were noted in the daily health observations for the original NADA studies or the PAMP Study. Results obtained from veterinary clinical observations were not consistent across studies or parity groups. Calluses of the knee were observed more frequently in sometribove-treated multiparous cows in the original NADA studies, but calluses are not considered to be an animal safety concern. Veterinary observations indicated more days of swollen knees in the PAMP Study primiparous cows treated with sometribove, but only in a very small number of cows for very few days. Thus, product labeling for sometribove no longer states that treated cows may have more lesions of the knee/carpal region.

Product labeling for sometribove continues to state that treatment is associated with more disorders of the foot region. However, the reference to this only being observed in multiparous cows was removed because daily health observations for the original NADA studies and the PAMP Study showed that the effect was also apparent in primiparous cows.

Increased lameness in sometribove-treated multiparous cows was not consistent across studies. Furthermore, an extensive evaluation of lameness in multiparous cows treated with sometribove for multiple lactations on commercial farms was conducted for the original NADA (see FOI Summary dated November 5, 1993, Section 6.f, Study #100-USA-COW-RJC-92-007). This study found that lameness was not increased in sometribove-treated multiparous cows compared to controls. No studies indicated that sometribove treatment was associated with lameness in primiparous cows. Thus, product labeling for sometribove does not state that treatment is associated with increased lameness. However, to maintain accuracy of the labeling, the statement “However, results of these studies did not indicate that use of POSILAC increased lameness” was removed because of the results observed for multiparous cows in the PAMP Study.

As a result of the reanalysis of data associated with the Musculoskeletal System, the product labeling cautions for this System were changed to the following:

> "Cows injected with POSILAC may have more enlarged hocks and disorders of the foot region."

Udder System

The original NADA concluded that there were no negative effects of sometribove treatment on the Udder System (FOI Summary, dated November 5, 1993, Section 6.k). Based on post-approval surveillance information, a labeling change was approved March 17, 1997, to include the following statement:

> "**Udder Edema**. POSILAC is approved for use beginning during the 9th or 10th week of lactation. Initiation of use in later lactation has been associated with increased risk of udder edema."

In the current reanalyses, no significant negative effects of sometribove treatment starting during the 9th or 10th week of lactation were found for the Udder System.

CONCLUSIONS (Udder System)

A statement regarding increased risk of udder edema if treatment is started later in lactation remains on product labeling.

Therapy

The original product labeling for sometribove stated:

> "Use of POSILAC is associated with increased frequency of use of medication in cows for mastitis and other health problems." (See FOI Summary dated November 5, 1993, Section 6.k.)

In the reanalysis of daily health observation data for the original NADA studies, primiparous cows treated with sometribove had significantly more "cows affected" than controls for therapeutic treatment of combined mastitis and non-mastitis conditions ("Total Days Medicated," Table 33). "Cows affected" was also significantly increased for mastitis therapy in primiparous cows treated with sometribove (Table 33). There was no significant effect of sometribove treatment on therapy given to multiparous cows in the original NADA studies, although a similar trend was observed (data not shown).

Table 33. Effect of Sometribove Treatment on Total Days Medicated for Primiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | **Study Period** | **Sometribove Dose (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Total Days Medicated – Primiparous Cows** | | | | | | | | |
| N | **Full Trtmt** | 87 | 34 | 95 | 34 | | | |
| Cows Affected (%)[d] | | 48.28 | 47.06 | 61.05 | 61.76 | **0.082** | **0.017** | 0.911 |
| Days Affected/100 Cow Days Risk[d] | | 0.8957 | 0.7479 | 1.1895 | 0.7869 | 0.554 | 0.545 | 0.682 |
| **Total Days Medicated for Mastitis – Primiparous Cows** | | | | | | | | |
| Cows Affected (%)[e] | **Full Trtmt** | 14.94 | 20.59 | 21.05 | 35.29 | | **0.039** | |
| Days Affected/100 Cow Days Risk[f] | | 0.3826 | 0.5558 | 0.5251 | 0.4641 | | 0.376 | 0.651 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.
[e] Exact Trend Test.
[f] Generalized Linear Mixed Model Analysis (dose as a continuous variable).

In the PAMP Study, therapeutic treatment for mastitis and non-mastitis conditions combined and therapy for non-mastitis conditions were significantly higher in primiparous cows treated with sometribove compared to controls in terms of both "cows affected" and "days affected" (Table 34). "Cows affected" was significantly increased in sometribove-treated multiparous cows compared to controls in the PAMP Study for therapeutic treatments combined, mastitis therapy, and non-mastitis therapy (Table 35).

Table 34. Effect of Sometribove Treatment on Total Days Medicated for Primiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Total Days Medicated – Primiparous Cows** | | | | |
| N | **Trtmt** | 209 | 210 | |
| Cows Affected (%)[b] | | 37.32 | 47.62 | **0.035** |
| Days Affected/100 Cow Days Risk[b] | | 0.6950 | 1.5600 | **0.024** |
| **Total Days Medicated for Non-Mastitis – Primiparous Cows** | | | | |
| Cows Affected (%)[b] | **Trtmt** | 32.06 | 40.95 | **0.058** |
| Days Affected/100 Cow Days Risk[b] | | 0.3910 | 0.9245 | **0.027** |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

Table 35. Effect of Sometribove Treatment on Total Days Medicated for Multiparous Cows in PAMP Study (Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | Probability A[a] |
|---|---|---|---|---|
| | | 0 | 500 | |
| **Total Days Medicated – Multiparous Cows** | | | | |
| N | **Trtmt** | 356 | 353 | |
| Cows Affected (%)[b] | | 42.13 | 52.41 | **0.012** |
| Days Affected/100 Cow Days Risk[b] | | 2.6127 | 2.4653 | 0.929 |
| **Total Days Medicated for Mastitis – Multiparous Cows** | | | | |
| Cows Affected (%)[b] | **Trtmt** | 23.03 | 28.61 | **0.086** |
| Days Affected/100 Cow Days Risk[b] | | 0.8533 | 1.1085 | 0.266 |
| **Total Days Medicated for Non-Mastitis – Multiparous Cows** | | | | |
| Cows Affected (%)[b] | **Trtmt** | 33.71 | 41.64 | **0.046** |
| Days Affected/100 Cow Days Risk[b] | | 1.9558 | 1.5363 | 0.400 |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis.

## CONCLUSIONS (Therapy)

Product labeling for sometribove continues to state that treated cows are likely to require more medication for mastitis and other health problems.

Miscellaneous - Body Temperature.

The original product labeling for sometribove stated:

> "Cows injected with POSILAC may experience periods of increased body temperature unrelated to illness. To minimize the effect, take appropriate measures during periods of high environmental temperature to reduce heat stress. Care should be taken to differentiate increased body temperature due to use of POSILAC from an increased body temperature that may occur due to illness." (See FOI Summary dated November 5, 1993, Section 6.m.3.)

These statements were based on analysis of body temperature data collected on a daily basis in the IM-Dose, IM/SC Bridging, and Multi-lactation Chronic Animal Toxicity Studies after elevated temperatures associated with a clinical health incident were eliminated from the datasets (see FOI Summary dated November 5, 1993, Section 6.m.3.) For the current reanalyses, all elevated body temperatures from the daily measurements obtained from the IM-Dose and IM/SC Bridging Studies were included, plus elevated body temperatures or fevers recorded in any of the other original NADA clinical studies and the PAMP Study. Body temperatures were also routinely recorded during physical examinations in the original NADA studies.

In the daily observation data for the original NADA studies, multiparous cows treated with sometribove had significantly more "cows affected" and "days affected" with elevated body temperatures than controls during the standardized treatment period (Table 36), and significantly more "cows affected" during the full treatment period (data not shown). Multiparous cows treated with sometribove in the original NADA studies also had elevated temperatures significantly more often than controls during routine physical examinations during mid-lactation (500 mg dose group) and the end of treatment (Table 37). No significant effects were observed for sometribove-treated primiparous cows in the original NADA studies or either parity group in the PAMP Study.

Table 36. Effect of Sometribove Treatment on Incidence of Elevated Body Temperature for Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Daily Health Observations).

| | Study Period | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Elevated Body Temperature – Multiparous Cows** | | | | | | | | |
| N | **Std Trtmt** | 201 | 52 | 212 | 52 | | | |
| Cows Affected (%)[d] | | 3.48 | 7.69 | 14.62 | 9.62 | **0.012** | **0.029** | 0.240 |
| Days Affected/100 Cow Days Risk[d] | | 0.0177 | 0.0427 | 0.1184 | 0.0595 | **0.001** | **0.002** | 0.148 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

Table 37. Effect of Sometribove Treatment on Incidence of Elevated Body Temperatures for Multiparous Cows in Original NADA Studies (Pooled IM-Dose, IM-Single, IM/SC Bridging, and SC-Dose Studies; Veterinary Physical Examinations).

| | Study Time | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Elevated Body Temperature – Multiparous Cows** | | | | | | | | |
| N | **180 dim** | 161 | 14 | 170 | 13 | | | |
| Cows Affected (%)[d] | | 3.11 | 0 | 12.94 | 0 | | **<0.001** | |
| N | **end trtmt** | 193 | 49 | 200 | 47 | | | |
| Cows Affected (%)[e] | | 3.63 | 14.29 | 6.00 | 21.28 | 0.269 | **0.058** | 0.897 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Exact Trend Test.
[e] Generalized Linear Mixed Model Analysis.

## CONCLUSIONS (Body Temperature)

The analyses conducted for the original NADA remain most appropriate for distinguishing effects of sometribove treatment on body temperature not associated with a clinical health incident. Those analyses found that treated cows tended to have higher body temperatures. The current reanalyses included all body temperatures and are consistent with the findings in the original NADA at least for multiparous cows. It was concluded that statements on product labeling related to effects of sometribove treatment on body temperature would remain.

**e. Reproduction**

Reproduction data were analyzed using three datasets:

First dataset: Original NADA IM Studies: Pooled IM-Dose, IM-Single, and IM-injected cows in IM/SC Bridging Studies

Second dataset: Original NADA SC-Dose Study

Third dataset: PAMP Study

Reproductive management of cows in the original NADA studies was previously described (see FOI Summary dated November 5, 1993, Section 6.i). Briefly, location-specific practices were followed for vaccination programs, sire selection, management of reproductive problems, and calving management. All cows received a veterinary examination to evaluate reproductive health before the start of the breeding program. All breeding was by artificial insemination. Estrus detection was by visual appraisal of standing estrus. Some locations also used heat detection aids such as heat mount detectors or tailhead chalking. Cows were monitored through pregnancy, and calves were weighed at birth. For the original NADA IM studies (including the IM/SC Bridging Study), cows could be bred between 40 and 170 DIM. Also, the IM study sites were allowed to use prostaglandins and gonadotropins to induce estrus and to use their normal location practices. For the original NADA SC-Dose Study, cows were bred between 60 and 305 DIM, and use of any medication to alter the normal estrus cycle was not allowed until after 120 DIM. No studies used timed breeding protocols.

For the PAMP Study, reproduction records were maintained according to each herd's practice. Cows were bred using artificial insemination except at the WF herd (see Table 5), where cows were bred by natural service. Only pregnancy palpation records were available for the WF herd. At all herds, cows were monitored through pregnancy, but calves were not weighed at birth.

In general, for the original NADA studies, cows had to complete at least two-thirds of the 252-day standardized treatment period to be included in analysis of reproduction variables. (See Sections 5.a, 6.c, 6.d, and 6.e in the FOI Summary dated November 5, 1993, for cows that started treatment in these studies but were excluded from analysis of reproduction variables.) Cows from the PAMP Study that were included in analysis are identified in Table 6. However, breeding dates were not known for cows at the WF site. Thus, cows from the WF site were excluded from analysis of variables that required knowledge of conception dates, such as days open, days between inseminations, treatment day of pregnancy, and days to first insemination.

Variables

Variables analyzed were in the original NADA (see FOI Summary dated November 5, 1993, Section 6.i, Table 65). Gestation length and calf birth weight are discussed in Sections 3.f and 3.g, respectively, of the current FOI Summary.

As described for the original NADA, the variables were analyzed over several separate study periods. For the pooled IM studies, where breeding started before the treatment period, analyses were conducted for the pretreatment period (0 to 60±3 DIM), during the first 28 days of treatment, day 29 of treatment through 170 DIM, 60±3 to 170 DIM, and 0 to 170 DIM. For the original NADA SC-Dose Study, analyses were conducted during the first 28 days of treatment, day 29 of treatment through 180 DIM, day 29 of treatment through 305 DIM, 60±3 to 180 DIM, and 60±3 to 305 DIM. Individual cows were only included in the periods of analysis for variables in which they were eligible, e.g., they were still on the study and were not already pregnant. All analyses were conducted both including and excluding cows that received any medication intended to alter the estrous cycle.

For the PAMP Study, analyses were conducted during the first 28 days of treatment, day 29 of treatment through the end of treatment, and the entire treatment period.

Methods of Analyses

Linear mixed model methods were used to analyze variables assumed to be normally distributed (e.g., days between inseminations) and generalized linear mixed model methods were used to analyze variables measured as counts or proportions. These methods are described in detail in Sections 3.b and 3.d. Reproductive variables recorded as counts were transformed {log(n+1)} and analyzed using the MIXED procedure if the generalized linear mixed model methods described in Section 3.b failed to converge.

To address particular questions related to specific reproductive variables, combined parity analyses were done. Fixed effects in these analyses included sometribove level, parity and the interaction of sometribove level and parity. Random effects in the full model included location, location by sometribove level, location by parity, and location by sometribove level by parity. These analyses were reported if the sometribove level by parity interaction was not significant ($P>0.1$).

For those variables observed only at a single location, the generalized linear model methods described in Section 3.d were used.

For event-time variables that were possibly censored, survival analysis (log-rank test using the LIFETEST procedure in SAS) was used to test for associations

between treatment levels and the response variables. The method used to compute the survival function estimates was Kaplan-Meier. Analyses were performed separately for each parity with location defined as a stratifying variable. A combined analysis across parities also was run for Days Open B, stratifying across location and parity. The TEST statement was used to assess the overall effect of treatment. For the IM and PAMP studies, where only two levels of sometribove (0 and 500 mg) were used, the TEST statement only included a linear term. For the SC study, where four levels of sometribove (0, 250, 500, and 750 mg) were available, the TEST statement included linear, quadratic, and cubic components. The probability associated with the overall Chi-square statistic was reported in the summary tables of analyses. For all censored reproductive variables, no tests for deviations from linearity were performed.

Effects were tested at the 10% level of significance. Biological interpretations of significant results considered overall incidence rate and consistency among treatment dose groups and studies.

RESULTS

As with the original NADA, results during the first 28 days of treatment were not substantially different from those observed during the remainder of the breeding period. Results during other periods were relatively consistent with the full breeding period while cows were on treatment. Thus, results are presented for the full breeding period while cows were on sometribove or control treatments, i.e., 60±3 to 170 DIM for the original NADA IM Studies, 60±3 to 305 DIM for the original NADA SC-Dose Study, and the entire treatment period for the PAMP Study. Finally, results were similar whether including or excluding cows that received any medication intended to alter the estrous cycle. Thus, results presented in the tables include cows given these medications.

Pregnancy rate and other variables related to conception rate were significantly affected by sometribove treatment. As with the original NADA, “pregnancy rate” was the variable used to best communicate this effect on product labeling (see below). “Days open” was also affected by sometribove treatment (see below). Effects of sometribove treatment on other variables that were addressed in original product labeling (cystic ovaries and multiple births) are also discussed below. Effects of sometribove treatment on gestation length and calf birth weight are discussed in Sections 3.f and 3.g, respectively.

Pregnancy Rate

The original product labeling for sometribove stated:

> "Use of POSILAC may result in reduced pregnancy rates in injected cows…" (See FOI Summary dated November 5, 1993, Section 6.i.)

Pregnancy rate (and related variables) was significantly reduced in primiparous cows treated with sometribove in the Pooled IM Studies (see Table 38). In the SC-Dose Study, there was no dose by parity interaction, and so effects of treatment were examined with parities pooled. The effect of dose of sometribove deviated from linearity (Table 39), with sometribove-treated cows tending to have lower pregnancy rates than control cows. There was no significant effect of sometribove treatment on pregnancy rate in the pooled parity analysis of the PAMP Study.

Table 38. Effect of Sometribove Treatment on Pregnancy Rate for Primiparous Cows in the Original NADA IM Studies (Pooled IM-Dose, IM-Single and [IM injected cows of] IM/SC Bridging Studies; 60±3 to 170 DIM).

| Variable | **Dose of Sometribove (mg every 14 d)** | | Probability A[a] |
|---|---|---|---|
| | 0 | 500 | |
| **Pregnancy Rate** (%)[b] | 90 ± 5 | 63± 7 | **0.037** |
| (ratio) | (37/41) | (30/48) | |

[a] Probability A is for treatment main effects.
[b] Generalized Linear Mixed Model Analysis; results reported as least-squares means ± standard error of least-squares means.

Table 39. Effect of Sometribove Treatment on Pregnancy Rate for Cows (Parities Pooled) in the Original NADA SC-Dose Study (60±3 to 305 DIM).

| Variable | **Dose of Sometribove (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Pregnancy Rate** (%)[d] | 92 ± 4 | 72 ± 6 | 81 ± 5 | 85 ± 6 | 0.121 | 0.473 | **0.063** |
| (ratio) | (56/61) | (44/61) | (48/59) | (49/60) | | | |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis; results reported as least-squares means ± standard error of least-squares means.

Days Open

The original product labeling for sometribove stated:

> "Use of POSILAC may result in … an increase in days open for first calf heifers." (See FOI Summary dated November 5, 1993, Section 6.i.)

Days open for cows becoming pregnant was significantly increased in primiparous cows treated with sometribove compared to controls in the Pooled IM Studies (Table 40, Days Open A). When including cows that did not conceive (days open set to the end of the breeding period), days open in primiparous cows treated with sometribove continued to be significantly increased compared to controls (Table 40, Days Open B).

Table 40. Effect of Sometribove Treatment on Days Open for Primiparous Cows in the Original NADA IM Studies (Pooled IM-Dose, IM-Single and [IM injected cows of] IM/SC Bridging Studies; 60±3 to 170 DIM).

| Variable | Dose of Sometribove (mg every 14 d) | | Probability A[a] |
|---|---|---|---|
| | 0 | 500 | |
| **Days Open A**[b,c] (n) | 90 ± 4 (37) | 104 ± 5 (30) | **0.070** |
| **Days Open B**[d,e] (n) | 99 ± 5 (42) | 130 ± 6 (49) | **<0.001** |

[a] Probability A is for treatment main effects.
[b] Average number of days from calving to conception for cows pregnant full term by 170 DIM.
[c] Mixed Model Analysis; results reported as least-squares means ± standard error of least-squares means.
[d] Average number of days from calving to conception for cows pregnant full term by 170 DIM, or censored at 170 DIM for cows not pregnant full term.
[e] Survival analysis, log rank test; results reported as raw means ± standard error of raw means.

In the SC-Dose Study, effects of treatment were examined with parities pooled because there was no dose by parity interaction. Days open was increased for sometribove-treated cows compared to controls only when including cows that did not conceive (Table 41, Days Open B), reflecting their decreased pregnancy rate. In the PAMP Study, there also was no dose by parity interaction. Sometribove-treated cows had significantly greater days open than controls, either including or excluding cows that did not conceive (Table 42).

Table 41. Effect of Sometribove Treatment on Days Open for Cows (Parities Pooled) in the Original NADA SC-Dose Study (60±3 to 305 DIM).

| Variable | Dose of Sometribove (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Days Open A**[d,e] (n) | 116 ± 7 (56) | 125 ± 8 (44) | 124 ± 7 (48) | 133 ± 7 (49) | 0.438 | 0.145 | 0.839 |
| **Days Open B**[f,g] (n) | 132 ± 9 (61) | 176 ± 11 (61) | 158 ± 11 (59) | 163 ± 10 (60) | **0.011** | | |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Average number of days from calving to conception for cows pregnant full term by 305 DIM.
[e] Mixed Model Analysis; results reported as least-squares means ± standard error of least-squares means.
[f] Average number of days from calving to conception for cows pregnant full term by 305 DIM, or censored at 305 DIM for cows not pregnant full term.
[g] Survival analysis, log rank test; results reported as raw means ± standard error of raw means.

Table 42. Effect of Sometribove Treatment on Days Open for Cows (Parities Pooled) in the PAMP Study (during treatment period).

| Variable | Dose of Sometribove (mg every 14 d) | | Probability A[a] |
|---|---|---|---|
| | 0 | 500 | |
| **Days Open A**[b,c] (n) | 139 ± 5 (382) | 150 ± 5 (355) | **0.063** |
| **Days Open B**[d,e] (n) | 183 ± 5 (457) | 200 ± 6 (445) | **0.052** |

[a] Probability A is for treatment main effects.
[b] Average number of days from calving to conception for cows pregnant full term.
[c] Mixed Model Analysis; results reported as least-squares means ± standard error of least-squares means.
[d] Average number of days from calving to conception for cows pregnant full term, or censored at the upper limit of breeding period for cows not pregnant full term.
[e] Survival analysis, log rank test; results reported as raw means ± standard error of raw means.

## Cystic Ovaries

The original product labeling for sometribove stated:

> "Use of POSILAC has also been associated with increases in cystic ovaries…" (See FOI Summary dated November 5, 1993, Section 6.i.)

The incidence of cystic ovaries in the original NADA studies and the PAMP Study was reevaluated in 1997. In the original NADA studies, increased cystic ovaries were primarily associated with IM injection of sometribove and not with SC injection. The PAMP Study further showed that the incidence of cystic ovaries was not increased in cows given sometribove by the SC route. Thus, the above statement was removed from product labeling (see FOI Summary dated December 27, 2001, Section 4.b).

In the current reanalysis, the incidence of cystic ovaries was re-examined (both "cows affected" and "cases" per 100 cow days). Incidence of cystic ovaries was not increased in cows treated with sometribove in the original NADA Pooled-IM Studies and the PAMP Study. In the Original NADA SC-Dose Study, effects of treatment were examined with parities pooled because there was no dose by parity interaction. There was a linear effect of sometribove dose on the "cows affected" with cystic ovaries (Table 43).

Table 43. Effect of Sometribove Treatment on Incidence of Cystic Ovaries in Cows (Parities Pooled) in the Original NADA SC-Dose Study (60±3 to 305 DIM).

| | **Sometribove Dose (mg every 14 d)** | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| **Cystic Ovaries** | | | | | | | |
| N | 61 | 61 | 59 | 60 | | | |
| Cows Affected[d] (%) | 19.67 | 26.23 | 27.12 | 36.67 | 0.277 | **0.077** | 0.801 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Generalized Linear Mixed Model Analysis.

Multiple Births

The original labeling for sometribove stated:

> "Cows injected with POSILAC …may have increased twinning rates." (See FOI Summary dated November 5, 1993.)

Rates of twinning (i.e., multiple births) in the original NADA studies and the PAMP Study were reevaluated in 1997. The studies showed that the incidence of multiple births was increased only in cows given sometribove by IM injection, not those injected SC. Thus, this statement was removed from product labeling (see FOI Summary dated December 27, 2001, Section 4.b).

In the current evaluation, the incidence of multiple births was significantly increased in multiparous cows treated with sometribove in the original NADA Pooled IM Studies (Table 44). A similar trend was noted in primiparous cows in this study (Table 44). However, there was no significant effect of sometribove treatment on the incidence of multiple births in the original NADA SC-Dose Study or the PAMP Study.

Table 44. Effect of Sometribove Treatment on Incidence of Multiple Births (full-term pregnancies) in the Original NADA IM Studies (Pooled IM-Dose, IM-Single and [IM injected cows of] IM/SC Bridging Studies; conceived 60±3 to 170 DIM).

| | **Dose of Sometribove (mg every 14 d)** | | |
|---|---|---|---|
| | 0 | 500 | Probability A[a] |
| **Primiparous Cows** | 2.9% (1/34)[b,c] | 20.8% (5/24) | 0.227 |
| **Multiparous Cows** | 1.2% (1/86) | 13.6% (11/81) | **0.071** |

[a] Probability A is for treatment main effects.
[b] Number of cows with multiple births (full-term pregnancies) divided by number of cows with full-term pregnancies.
[c] Generalized Linear Mixed Model Analysis.

## CONCLUSIONS

Although not significant in all studies, pregnancy rates were reduced in sometribove-treated cows in studies where the product was injected either IM or SC. Product labeling continues to state that cows treated with POSILAC may have reduced pregnancy rates.

"Days open" was increased in cows treated with sometribove. Only primiparous cows were affected in the original NADA Pooled IM studies. However, both parity groups were affected in the original NADA Pooled SC studies and the PAMP Study. In the Pooled SC studies, the effect was only observed when including the cows that did not conceive in the analysis. However, in the Pooled IM studies and PAMP Study, the effect also was evident when using only the cows that conceived to full-term pregnancies. Product labeling continues to state that sometribove-treated cows may have increased days open, but the reference to this only being observed in primiparous cows was removed.

These reanalyses support the previous decisions to remove labeling cautions regarding cystic ovaries and multiple births. These variables were not consistently affected by sometribove treatment. These variables remain off of product labeling.

Product labeling continues to advise users to have a comprehensive and ongoing herd reproductive health program in place before using POSILAC.

**f. Gestation Length**

The original product labeling for sometribove stated:

> "Cows injected with POSILAC may have small decreases in gestation length…" (See FOI Summary dated November 5, 1993, Section 6.l.)

The effect of sometribove treatment on gestation length in treated cows was reevaluated using three datasets:

First dataset: Original NADA 4-Dose Studies: Pooled IM-Dose and SC-Dose Studies

Second dataset: Original NADA SC-Dose Study

Third dataset: Original NADA SC-Dose and PAMP Studies: Pooled SC-Dose and PAMP Studies

The WF location of the PAMP Study was excluded from analysis because cows were bred by natural service and accurate conception dates could not be determined.

Gestation length was calculated as the day of calving minus the day of conception for full-term calves (i.e., gestation length ≥250 and ≤314 days), including calves that were conceived in the pretreatment period for the IM-Dose and PAMP Studies. Only calves born as single births (e.g., not twins) were included in the evaluation.

Gestation length was analyzed using linear mixed models (MIXED) as described under Section 3.b.

RESULTS

Sometribove treatment of primiparous cows had no effect on gestation length in any of the three datasets. In multiparous cows, sometribove treatment was associated with shorter gestation lengths in the Pooled IM-Dose and SC-Dose Studies and the SC-Dose Study evaluated alone (Table 45). However, when combining data from the SC-Dose and PAMP Studies, there was no significant effect of sometribove treatment (Table 45).

Table 45. Effect of Sometribove Treatment on Gestation Length for Single Births in Multiparous Cows.

| Dataset | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|
| | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| Pooled IM-Dose & SC-Dose Studies | 282.2[d] ± 1.4 (42[e]) | 276.8 ± 1.5 (35) | 277.1 ± 1.5 (37) | 277.6 ± 1.5 (32) | **<0.001** | **0.003** | **0.010** |
| SC-Dose Study | 281.7 ± 1.8 (29) | 277.7 ± 1.8 (26) | 276.5 ± 1.8 (25) | 278.4 ± 1.9 (23) | **0.011** | **0.037** | **0.043** |
| Pooled SC-Dose & PAMP Studies | 279.9 ± 0.5 (216) | 278.0 ± 1.4 (26) | 279.7 ± 0.5 (195) | 278.6 ± 1.5 (23) | 0.518 | 0.588 | 0.404 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Mixed Model Analysis; results are reported as least-squares means (days) ± standard errors of least-squares means.
[e] Number of calves.

CONCLUSIONS

Sometribove treatment had no effect on gestation length in primiparous cows. When including data from the large PAMP Study in analyses, there was no effect of treatment on gestation in multiparous cows. Thus, statements relative to effect of sometribove treatment on gestation length were removed from product labeling.

## g. Calf Birth Weight

The original product labeling for sometribove stated:

> "Cows injected with POSILAC may have small decreases in …birth weight of calves…" (See FOI Summary dated November 5, 1993, Section 6.l.)

The effect of sometribove treatment on birth weight of calves born to treated cows was reevaluated using two datasets:

First dataset: Original NADA 4-Dose Studies: Pooled IM-Dose and SC-Dose Studies

Second dataset: Original NADA SC-Dose Study

The PAMP Study was excluded from analysis because calves were not weighed.

Birth weight was evaluated for all full-term births, and also for full-term single births only (i.e., not twins). Calves that were conceived during the pretreatment period of the IM-Dose Study were included in the analysis.

Calf birth weight was analyzed using linear mixed models (MIXED) as described under Section 3.b.

RESULTS

Sometribove treatment of primiparous cows in the Pooled IM-Dose and SC-Dose Studies tended to reduce birth weights when considering all births, although the dose effect deviated from linearity (Table 46). When considering only single births, there was no effect (Table 46). Results with only the SC-Dose Study demonstrated no effect of sometribove treatment on birth weights in primiparous cows (Table 46).

Table 46. Effect of Sometribove Treatment on Birth Weights in Primiparous Cows.

| Dataset | | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| Pooled IM-Dose & SC-Dose Studies | All births | 40.1[d] ± 2.5 (30[e]) | 35.5 ± 2.2 (26) | 37.5 ± 2.4 (30) | 37.8 ± 2.2 (32) | 0.151 | 0.423 | **0.075** |
| | Single births | 43.1 ± 2.4 (26) | 42.6 ± 2.5 (18) | 41.7 ± 2.4 (26) | 42.3 ± 2.4 (25) | 0.843 | 0.487 | 0.834 |
| | | | | | | | | |
| SC-Dose Study | All births | 37.3 ± 3.5 (23) | 36.1 ± 3.2 (18) | 37.9 ± 3.2 (23) | 37.8 ± 3.3 (25) | 0.933 | 0.723 | 0.869 |
| | Single births | 42.2 ± 2.6 (21) | 41.5 ± 2.7 (16) | 40.6 ± 2.7 (21) | 41.2 ± 2.6 (22) | 0.862 | 0.483 | 0.861 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Mixed Model Analysis; results are reported as least-squares means (kg) ± standard errors of least-squares means.
[e] Number of calves.

Calves of multiparous cows treated with sometribove in the Pooled IM-Dose and SC-Dose Studies that had single births had significantly lower birth weights than calves from control cows (Table 47). When considering all births, there was no significant effect (Table 47). Results from the SC-Dose Study alone demonstrated no effect of sometribove treatment on birth weights in multiparous cows (Table 47).

Table 47. Effect of Sometribove Treatment on Birth Weights in Multiparous Cows.

| Dataset | | Sometribove Dose (mg every 14 d) | | | | Probability | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 250 | 500 | 750 | A[a] | B[b] | C[c] |
| Pooled IM-Dose & SC-Dose Studies | All births | 37.9[d] ± 1.9 (50[e]) | 37.0 ± 2.3 (39) | 36.1 ± 2.3 (40) | 39.6 ± 2.0 (39) | 0.339 | 0.454 | 0.301 |
| | Single births | 46.0 ± 2.0 (42) | 44.1 ± 2.0 (35) | 41.8 ± 2.0 (36) | 43.7 ± 2.0 (32) | **0.048** | **0.054** | 0.123 |
| | | | | | | | | |
| SC-Dose Study | All births | 37.7 ± 2.1 (37) | 34.9 ± 2.9 (28) | 35.0 ± 2.4 (28) | 39.2 ± 2.2 (30) | 0.394 | 0.542 | 0.311 |
| | Single births | 45.4 ± 2.4 (29) | 43.9 ± 2.5 (26) | 40.5 ± 2.5 (24) | 43.1 ± 2.5 (23) | 0.112 | 0.105 | 0.175 |

[a] Probability A is for treatment main effects.
[b] Probability B is for linear trends.
[c] Probability C is for deviation from linear trends.
[d] Mixed Model Analysis; results are reported as least-squares means (kg) ± standard errors of least-squares means.
[e] Number of calves.

CONCLUSIONS

Sometribove treatment reduced calf birth weight only when data from the IM-Dose Study were included in the analysis, and the effect was not consistent for primiparous and multiparous cows. There was no significant effect of treatment on cows in the SC-Dose Study, which used the approved injection route. Consequently, the statement suggesting an effect of sometribove treatment on calf birth weight was removed from product labeling.

## *4. HUMAN SAFETY:*

This supplemental approval does not affect this section of the FOI Summary for the original approval. Refer to the FOI Summary dated November 5, 1993.

## *5. AGENCY CONCLUSIONS:*

The data submitted in support of this supplemental NADA 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 (sometribove zinc suspension) administered by subcutaneous injection is safe and effective for increased production of marketable milk in healthy lactating dairy cows. Multiparous as well as primiparous cows treated with sometribove have increased days open. Sometribove treatment does not decrease gestation length or calf birth weight. The incidence of retained placenta is not increased when cows are treated with sometribove. Sometribove treatment does not increase the incidence of digestive disorders or periods of "off-feed" in treated cows. Treated cows do not have more lesions of the knee, but primiparous and

multiparous cows have more disorders of the foot region, not just multiparous cows. Product labeling has been changed to reflect these conclusions.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instructions in plain language. The drug product is not a controlled substance. Thus, the NADA retains OTC status, and the 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 is not eligible for generic copying because it is a drug primarily manufactured using biotechnology.

This supplemental new animal drug application is a Category II change (21 CFR 514.106(b)(2)). The approval of this change required a reevaluation of certain safety data in the parent application with respect to reanalyzing cow health and reproduction data using mixed model analyses. Effectiveness and human safety data were not reevaluated.

POSILAC is under the following U.S. patent numbers:

| U.S. Patent Number | Date of Expiration |
|---|---|
| 4,985,404 | January 15, 2008 |
| 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 |

## *6. ATTACHMENTS:*

Facsimile labeling is attached as follows:

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