

Hypoestrogenic Symptoms

Table 14 (reproduction of data from Table 29, page 85 volume 1) presents the Sponsor's analyses of the hypoestrogenic side-effects of nafarelin 400 mcg and leuprolide 3.75 mg. The percentage of days with the event was defined as the percentage over the active treatment period of the days recorded in the diary with the specific event. The median percentage of days of bleeding were 8% and 6%, respectively, for nafarelin and leuprolide treatment ($p=0.01$). Fifty nine percent of patients receiving nafarelin reported heavy bleeding compared to 38 % of patients treated with leuprolide ($p=0.08$). The median percentage of days with hot flashes were 66% and 91%, respectively for nafarelin and leuprolide treatment ($p < 0.001$). Patients in the nafarelin group reported less severe hot flashes than patients given leuprolide ($p=0.065$). The leuprolide group had a shorter time to the occurrence of the hot flash (median-13 days) than patients in the nafarelin group (median-27days).

Table 14
Number (%) of Patients with Hypoestrogenic Symptoms During the Treatment Phase-All Efficacy Patients

	NAFARELIN 400 MCG	LEUPROLIDE 3.75 MG	P-VALUE
Number of Patients	98	93	
Bleeding No. with Bleeding Median Percent Days with Event	98 (100%) 8.2%	93 (100%) 5.9%	1.00 ¹ 0.011 ²
Hot Flashes No. with Hot Flashes Median % Days with Event	95 (97%) 66%	93 (100%) 91%	0.247 ¹ <0.001 ²
Vaginal Dryness No. with Vaginal Dryness Median % Days with Event	77 (79%) 24%	69 (74%) 34%	0.499 ¹ 0.178 ²
Mood Swings No. with Mood Swings Median % Days with Event	91 (93%) 45%	87 (94%) 42%	1.00 ¹ 0.802 ²
Headaches No. with Headache Median % Days with Event	94 (96%) 25%	91 (98%) 26%	0.683 ¹ 0.713 ²
Sleep Problem No. with Sleep Problem Median % Days with Event	94 (96%) 28%	89 (96%) 34%	1.00 ¹ 0.134 ²
Muscle and Joint Aches No with Muscle and Joint Ache Median % Days with Event	95 (97%) 32%	89 (96%) 37%	0.715 ¹ 0.784 ²

1. The treatment difference is tested by Fisher's exact test
2. The treatment difference is tested by a Wilcoxon rank sum test.

Reviewer's Comment: The original protocol states that the percent of patients reporting hypoestrogenic symptoms would be analyzed using Cochran-Mantel-Haenszel chi-square test. A chi-square test of proportions at a two-tailed alpha of 0.05 was stated to have 84% power to detect a treatment group difference in hypoestrogenic symptoms where 20% of patients in one treatment group and twice that (40% of patients) in the other group have these symptoms. The protocol did not pre-specify an analysis to demonstrate either equivalence or superiority. With the exception of vaginal dryness, greater than 90% of patients in both treatment arms displayed hypoestrogenic symptoms. The Sponsor, therefore, based their analyses on median % days with the event or mean % days with the event (analyses not shown). Of the 7 symptoms analyzed, only two showed a difference, one statistically favoring Synarel (hot flashes, $p < 0.001$) and one favoring leuprolide (bleeding, $p = 0.011$).

Further, the same concerns about a study of the lowest approved dose of nafarelin vs. the only approved dose of leuprolide also apply here. It is likely that if the higher dose of nafarelin had also been studied, the degree of suppression in estradiol levels would also have been greater and the degree of the hypoestrogenic symptoms would have changed appropriately, i.e. less bleeding and more hot flushing. In fact, in studies ICM 1010 and ICM 951 (chronic dosing studies of nafarelin submitted to original NDA, 19-886), women were given several intranasal doses of nafarelin and followed for 3 and 6 months, respectively. The 125 mcg/day and 250 mcg/day doses induced oligomenorrhea, while women receiving 1000 mcg/day were amenorrheic throughout the treatment period. Hot flushes were more significant in the 1000 mcg/day group.

In summary, all of the adverse events (BMD loss, hot flashes, withdrawal bleeding) appear to exhibit a dose-response relationship to treatment. Only by studying and comparing the full dosage range of nafarelin to leuprolide could meaningful claims of superiority on these endpoints be made.

3.11 Safety Analyses

Safety parameters included adverse events (AEs) and discontinuations to do AEs, changes in the physical exam and lab values and pregnancy.

Adverse events

Of the 208 patients in the all-subjects treated group (Sponsor specified safety patients), 186 (89%) reported at least one adverse event; 90% of the nafarelin-treated patients and 88% of the leuprolide-treated patients reported at least one event. There were 114 patients (55%) who reported adverse events during treatment that were probably/possibly study drug-related.

Reviewer's Comments: Both GnRH agonists at the dosages used in this study are approved for the indication of the treatment of endometriosis. The type and incidence of adverse events was similar to that reported in the label of both approved products. There were no unexpected or new safety events of concern noted in this trial.

Severe adverse events (SAEs)

Fifteen percent of all patients (nafarelin-14% leuprolide-15%) reported events that were classified by the investigators as severe. The severe events that were possibly/probably drug-related included 14 % of patients in the nafarelin group and 20 % of patients in the leuprolide group. There were no major cerebrovascular or cardiovascular events. One death occurred during the study: patient (nafarelin group) died from smoke inhalation during an accidental house fire. SAEs possibly/probably related to study drugs are listed on the next page (from Table 37 page 107, volume one).

Table 15
Severe Adverse Events During Six Months of Treatment-Possibly/ Probably Related
To Drugs

URINARY/ REPRODUCTIVE TRACT		
	Nafarelin	Leuprolide
Breast pain	1	0
Endometrial neoplasia	1	-
Urogenital pain	0	1
Vaginitis	0	1
Vulvovaginitis	-	1

OTHER BODY SITES		
	Nafarelin	Leuprolide
Abdomen enlarged	1	0
Abdominal pain	1	0
Abnormal vision	-	1
Acne	2	0
Anxiety	-	1
Arthralgia	0	2
Body Pain	2	3
Depression	2	2
Dry Skin	1	-
Emotional lability	1	2
Flu syndrome	1	-
Headache	5	4
Joint disorder	1	0
Leg cramp	1	-
Libido decreased	1	1
Migraine	1	1
Paresthesia	1	2
Peripheral Edema	2	
Pelvic pain	1	1
Pharyngitis	0	0
Pruritis	1	0
Rash		
Respiratory infection	2	
Special sense infection		2
Urticaria	1	-
Vasodilatation	0	2

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OTHER BODY SITES		
Vomiting	1	-

Reviewer's comments: The most common severe adverse event was headache and the incidence of this event between the two treatment groups did not differ greatly. Other severe adverse events were quite rare.

Discontinuations Secondary To Adverse Events During Treatment

A total of 20 patients (10%) terminated the study medication prematurely because of adverse events (nafarelin-7, leuprolide -13). The following table lists discontinuations due to AEs:

Table 16

Discontinuations due to Adverse Events-Treatment Phase¹

Treatment	Patient	Days on Treatment ²	Adverse Event		Severity	Relationship to study drug ³
			verbatim	preferred term		
nafarelin 400 mcg		125	R leg pain ⁴	Pain	Severe	Probably
		30	Abdominal swelling ⁴ Breast tenderness ⁴ Headaches, sinus Multiple joint swelling/redness ⁴ Muscle joint pain ⁴ Pitting edema-calves/ankles ⁴	Abdomen enlarged Breast Pain Headache joint disorder Pain Peripheral edema	Severe Severe Moderate Severe Moderate Severe	Possibly Possibly Possibly Possibly Possibly Possibly
		190	Bloating Headaches ⁴ Neck pain ⁴ Vaginal irritation	Flatulence Headache Neck pain Vaginitis	Moderate Severe Severe Moderate	Probably not ^{3d} Probably not ^{3d} Probably not ^{3d} Probably not ^{3d}
		174	Pain with BM Decreased appetite Severely tired Decreased breast Clinical depression Trouble voiding Decrease urination Pelvic pain ⁴ Bleeding with BM	Abdominal pain Anorexia Asthenia Breast atrophy Depression Dysuria Oliguria Pelvic pain Rectal hemorrhage	Moderate Severe Severe Mild Severe Moderate Moderate Severe Moderate	Probably not ^{3d} Probably not ^{3d} Probably not ^{3d} Possibly Probably not ^{3d} Possibly Probably not ^{3d} Probably not ^{3d} Probably not ^{3d} Probably not ^{3d}
		200	Major depressive Disorder ⁴ Multiple personality disorder ⁴	Depression Schizophrenic Reaction	Severe Severe	Probably not ^{3d} Probably not ^{3d}
		84	Diarrhea Headaches ⁴ Upper respiratory infection Nausea Urinary frequency	Diarrhea Headache Infection Nausea Urinary frequency	Moderate Severe Moderate Moderate Mild	Possibly Probably Probably not ^{3d} Possibly Possibly

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			Vomiting	Vomiting	Moderate	Possibly
		86	Mood swings ⁴ Severe pelvic pain ⁴	Emotional lability Pelvic pain	Severe Severe	Possibly Probably not ^{5a}
Leuprolide 3.75m		92	Dizziness ⁴ Mood Swings ⁴ Nausea Stiffness in wrists ⁴ Edema hands & feet ⁴ Rash ⁴	Dizziness Emotional lability Nausea Pain Peripheral edema Rash	Mild Severe Mild Moderate Moderate Moderate	Possibly Possibly Possibly Possibly Probably not ^{5a}
		148	Severe depression ⁴ Pain-muscles, tendons, joints ⁴ Vaginal pain ⁴ Numbness, tingling of hands ⁴ Suicidal Ideations ⁴	Depression Pain Pain Paresthesia Psychotic Depression	Severe Severe Severe Severe Severe	Possibly Possibly Possibly Possibly Possibly
		86	Diarrhea Dx ulcer ⁴	Diarrhea Peptic ulcer	Mild Moderate	Probably not ^{5a} Probably not ^{5a}
		58	Anxiety ⁴ Nervous ⁴	Anxiety Nervousness	Severe Severe	Possibly Possibly
		130	Back pain Severe Pelvic pain ⁴	Back Pain Pelvic Pain	Severe Severe	Probably not ^{5b} Probably not ^{5b}
		62	Headaches (sinus) ⁴ Insomnia ⁴ Hot flashes	Headache Insomnia Vasodilatation	Moderate Severe Severe	Probably Probably Probably
		92	Increased dysfunctional bleeding ⁴	Hemorrhage	Severe	Probably not ^{5c}
		62	Insomnia ⁴ Sinus congestion	Insomnia Sinusitis	Severe Moderate	Possibly Probably not ^{5d}
		29	Pain behind eyeballs ⁴ Headaches Neck Pain	Eye Pain Headache Neck pain	Moderate Moderate Moderate	Probably Probably Probably
		123	Numbness & tingling Lt. foot ⁴ Numbness all fingers ⁴	Paresthesia Paresthesia	Moderate Moderate	Probably Possibly
		92	Sleep problems ⁴ Hot flashes ⁴	Insomnia Vasodilatation	Severe Severe	Probably Probably
		31	Dizziness ⁴ Mood Swings ⁴ Headaches ⁴ Lack of sexual desire ⁴ Numbness R arm & hand ⁴	Dizziness Emotional lability Headache Libido decreased Paresthesia	Mild Severe Severe Moderate Moderate	Probably Probably Probably Possibly Possibly
		114	Joint pain ⁴ Mood swings ⁴ muscle aches ⁴ Hot flashes ⁴	Arthralgia Emotional lability Myalgia Vasodilatation	Severe Moderate Moderate Moderate	Possibly Probably Probably Probably

1. Treatment phase included a 30-day observation period after the end of active treatment. Included were patients who discontinued treatment but continued in the study through the follow-up period.
2. Number of days on study drug at time of termination.
3. Based on investigator's assessment
4. Primary reason for discontinuation
5. If designated as probably not related to study drug, reasons:
 - a- present before study

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- b- primary disease
- c- concomitant medications
- d- intercurrent illness
- e- other

Reviewer's Comments- Three of the 7 patients who discontinued due to adverse events had events that were categorized as probably/possibly related to study drug. These events included abdominal enlargement, breast pain, joint disorders, peripheral edema, pain and headache. Three had adverse events which were classified as probably not related to the drug and the remaining patient discontinued due to events in both of these categories. Of the 13 patients who discontinued from leuprolide, 9 discontinued secondary to events possibly/probably related to the drug. These events included anxiety, dizziness, depression, psychotic depression, mood swings, nervousness, pain, headaches, insomnia, eye pain, paresthesias and joint pain. Three patients discontinued secondary to events that were probably not related to the drug. One patient on leuprolide discontinued secondary to adverse events under both classifications. Overall, the number of patients discontinuing study drug was small and was comparable between arms.

**Table 17
Patients Discontinuing Due to Adverse Event in the Post-treatment Follow-Up¹**

Treatment	Patient	Days on Treatment ²	Adverse Events (verbatim)	Adverse Events (preferred term)	Severity	Relationship to Study Drug ³
nafarelin 400 mcg		181	Hysterectomy with left salpingo-oophorectomy ⁴	Reaction unevaluable	Severe	Probably not ^{5a}
		180	Dysmenorrhea ⁴ Pelvic Pain ⁴	Dysmenorrhea Pelvic Pain	Moderate	Probably not ^{5b} Probably not ^{5b}
		181	Diarrhea Severe dysmenorrhea ⁴ Nausea Hives Vomiting	Diarrhea Dysmenorrhea Nausea Urticaria Vomiting	Moderate Severe Moderate Mild Moderate	Probably not ^{5d} Probably not ^{5d} Probably not ^{5d} Probably not ^{5d} Probably not ^{5d}
leuprolide 3.75 m		183	Large left leg bruise ⁴	Ecchymosis	Mild	Probably not ^{5a}
		185	Abdominal pain ⁴	Abdominal pain	Severe	Probably not ^{5b}
		174	Injury to ribs (Lt.) Extreme head pain Severe pelvic pain ⁴	Accidental injury Headache Pelvic pain	Moderate Severe Severe	Probably not ^{5b} Possibly Probably not ^{5b}

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1. Includes patients who completed 6 months of treatment but who dropped out during post-treatment follow-up
2. Number of days on study drug
3. Based on investigator's assessment
4. Primary reason for discontinuation
5. If designated as probably not related to study drug, reasons:
 - a- present before study
 - b- primary disease
 - c- concomitant medications
 - d- intercurrent illness
 - e- other

Reviewer's Comments: A review of patients who discontinued in the post-treatment phase with reasons related to the primary disease was performed. Patient (nafarelin arm) showed improvement of symptoms during the treatment phase. However, sometime after the month 9 follow-up visit, severe pelvic pain returned and the patient requested a TAH/Lt. Salpingo-oophorectomy for endometrioma. Patient (nafarelin arm) had relief of her symptoms during treatment. By month 6, she was asymptomatic. Symptoms returned in the follow-up period and before the 12 month visit, her pelvic pain (mod) and dysmenorrhea (mod) led to scheduling of a TAH/BSO. Patient (nafarelin arm) had relief during treatment, albeit, not consistently. She had severe dysmenorrhea on baseline and became amenorrheic during treatment. By month 9 of the follow-up, however, severe dysmenorrhea had returned and she was scheduled to receive a pre-sacral neurectomy. Patient (leuprolide) completed 175 days on study medication, but subsequently had a hysterectomy scheduled for severe pelvic pain. The case report forms were not reviewed and, therefore, the extent of her relief during treatment cannot be commented upon.

Overall, three nafarelin and one leuprolide patient were reported to have required surgery because of the return of their symptoms during the study follow-up.

Changes in lab values

There were no premature terminations due to laboratory abnormalities.

Changes in physical exam

There were no significant changes in physical exam over time.

Pregnancy

No pregnancies occurred in patients receiving active treatment. Seventeen pregnancies occurred during the post-treatment follow-up: Twelve were in patients who had been treated with nafarelin, and five were in patients treated with leuprolide.

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4.0 Reviewer's assessment of safety and efficacy.

The Sponsor's objective in this study was to compare two approved drugs, intranasal nafarelin and leuprolide depot, for endometriosis symptom relief, bone mineral changes, estradiol levels and hypoestrogenic effects. A single study was submitted for consideration. Endometriosis sign and symptom relief was the only endpoint for which labeling claims were made prospectively. The Sponsor stated that equivalence would be claimed if nafarelin had an improvement rate within 20 % of the improvement rate of leuprolide for each of five symptoms and signs.

For the subjective symptoms of dysmenorrhea, dyspareunia and pelvic pain, equivalence was demonstrated. However, for the two physician assessed signs of pelvic induration and tenderness, equivalence was not demonstrated.

Equivalency claims or superiority claims were not stated prospectively for bone mineral changes (or estradiol levels) or hypoestrogenic symptoms. In a *post hoc* analysis, the Sponsor makes superiority claims based on bone mineral changes and median percent days with hot flushing. This single study compares the lowest approved dose of nafarelin with the only approved dose of leuprolide, and does not support these claims. In order to obtain a superiority claim for bone mineral density, the Sponsor will have to do at least one additional robust study. Superiority criteria should be stated prospectively and patients should be able to titrate their nafarelin dose upward as per the approved labeling. The results of protocol Lab/Naf 610 could be considered supportive. These same considerations apply to any claims related to the hypoestrogenic side-effects of the two drugs.

There are no new safety issues with nafarelin 400 mcg beyond those already addressed in the label.

5.0 Comments on the proposed labeling

The label as submitted by the Sponsor is not acceptable. The Reviewer suggests the following alternative labeling under the Clinical Pharmacology:

In a single controlled clinical trial, intranasal Synarel (nafarelin acetate) at a dose of 400 micrograms per day was shown to be clinically comparable to intramuscular leuprolide depot, 3.75 mg monthly, for the treatment of the symptoms (dysmenorrhea, dyspareunia and pelvic pain) associated with endometriosis.

Under Adverse Reactions, the following wording is suggested:

After six months treatment with Synarel, bone mass as measured by dual x-ray bone densitometry (DEXA) decreased by 3.2%. Mean total vertebral mass, re-examined by DEXA six months after completion of treatment, was 1.4% below pretreatment.

6.0 Recommendations for regulatory action

The Reviewer recommends approval of the supplement with the above labeling only.

7.0 References

- 1.) Olive, D.L., Schwartz, L.B., Endometriosis, *New England Journal of Medicine* 328:1759, 1993
- 2.) Gambone, J.C., DeCherney, A.H., Surgical treatment of minimal endometriosis., *New England Journal of Medicine*, 337(4):269, 1997
- 3.) Speroff, L., Glass, R.H., Kase, N.G., *Clinical Gynecologic Endocrinology and Infertility*, 5th edition, Williams and Wilkins, Baltimore, MD, 1994, p. 853
- 4.) Meldrum, D.R., Clinical management of endometriosis with luteinizing hormone-releasing hormone analogues. *Seminars Reprod. Endocrinol.* 3:371, 1985

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- 5.) Lemay A., Sandow, J., Bureau, M., Maheux, R., Fontaine, J-Y., Merat, P., Prevention of follicular maturation in endometriosis by subcutaneous infusion of Luteinizing hormone-releasing hormone agonist started in the luteal phase, Fertility and Sterility 49:410, 1988

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Shelley R. Slaughter, MD, Ph.D.
Medical Officer, DRUDP

8 - 12/22/98

Concurrence:

Marianne Mann, MD., Deputy Director, DRUDP

J concur - M Mann M.D.

cc: Marianne Mann, MD
Lisa Rarick, MD
Shelley R. Slaughter, MD Ph.D.
David Hoberman,
Division File NDA 19,886

12/22/98.

ADDENDUM TO MEDICAL CONSULT

NOV 25 1998

DRUG: Nafarelin acetate

NDA: 19-886/s-013

SPONSOR: Searle

CONSULT REQUESTED BY: HFD-580

SUBJECT OF CONSULT: Study Report NAF610, Evaluation of bone mineral density data (originally submitted 12/22/97)

DATE: 11/24/98

In my original consult dated 9/23/98, I concluded that the submitted data on bone mineral density (BMD) indicated that women who received 6 months of 3.75 mg/month of leuprolide had a statistically significantly greater reduction in BMD compared with women who received 6 months of 200 ug bid of nafarelin. I still believe that this is true.

However, my comments about labeling changes should not be construed as a recommendation for the approval of this supplemental NDA. This decision obviously rests with the consulting division.

Recent discussions with HFD-580 have raised questions about the overall relevance of the BMD findings from NAF610. One point relates to the 400-ug-bid dose of nafarelin, a dose that is also approved for the treatment of endometriosis, but was not included in study NAF610. It was suggested that a second trial be conducted in which the BMD effects of 200 ug bid and 400 ug bid of nafarelin are compared with leuprolide.

Taking into consideration all things discussed with members of HFD-580, I agree that a second trial, which includes the 400 ug bid dose of nafarelin, would be of great value, both from a scientific and regulatory standpoint.

ES *11/27/98*
Eric Colman, MD

cc: HFD-510 Consult file
HFD-580 Kish/Mann
HFD-580 Div. file

Rich

NOV 4 1998

MEDICAL CONSULT

NDA 19-886/S-013

REQUESTED BY: DRUDP, HFD-580

DRUG: Nafarelin acetate

SPONSOR: Searle

SUBJECT OF CONSULT: Study Report NAF610, Evaluation of bone mineral density data
submitted 12/22/97

MATERIAL RECEIVED: Nafarelin product labeling and final report of study NAF610

DATE CONSULT RECEIVED: 9/22/98

DATE OF REVIEW: 9/23/98

BACKGROUND

The Division of Reproductive and Urological Drug Products has requested that the Division review the bone mineral data from a study that compared multiple effects of nafarelin to those of leuprolide in patients with endometriosis.

Nafarelin is an agonistic analog of gonadotropin-releasing hormone (GnRH) that is indicated for the management of endometriosis.

Based on the results of study NAF610, the company has requested a labeling change within the Clinical Pharmacology section. The relevant segment of the proposed labeling states: "Patients on both treatments experienced bone mineral density loss as assessed by L1-L4 dual x-ray bone densitometry (DEXA). At the end of the 6 month treatment, bone loss was less in the nafarelin group than in the leuprolide group (3.2% vs. 4.5%, $p=0.002$). Bone loss was substantially reversed during the post-treatment period in both groups."

PROTOCOL REVIEW

Title: Comparison of nafarelin intranasal vs. leuprolide depot intramuscular in patients with endometriosis.

Study Period: October 1991 – June 1994

Objectives: The primary objectives of this study were to compare nafarelin intranasal and leuprolide depot for endometriosis symptom relief, bone mineral changes, estradiol levels, and hypoestrogenic effects.

Design: A 12-month, multicenter, single-blind (patient and if possible the investigator), double-placebo, randomized (1:1), parallel study. Each patient was treated with active drug for 6 months and followed for an additional 6 months. Patients were randomized to either 200 ug bid of nafarelin spray or 3.75 mg of leuprolide depot injection q monthly. Patients also received a placebo version of the spray or monthly injection.

Patient Population: Women between the ages of 18 to 46 years with a diagnosis of endometriosis confirmed by laparoscopy or laparotomy within the previous 18 months. Exclusion criteria included: recent use of GnRH agonists, glucocorticoids, oral contraceptives, BMD > 2sd below normal mean for age.

Methods: DEXA (Hologic or Lunar scanner) measured L1-L4 BMD at baseline, Month 6, and Month 12. Longitudinal variations in BMD were subject to correction formulas as described by Lu. Relief of symptoms associated with endometriosis was determined by both patient and investigator assessments. Symptom severity included self-reported symptoms of dysmenorrhea, dyspareunia, and non-pelvic pain as well as pelvic tenderness and induration recorded during pelvic examination. For a subset of patients, hypoestrogenic status was evaluated by levels of estradiol and by measurement of body temperature. For BMD measurements, the end of treatment window was defined as between 14 days prior to the last dose up to 45 days after the last dose.

Statistical Analyses: The sponsor claims that the study had 84-90% power to detect a 4-6% treatment group difference in BMD (two-tailed significance test at the 0.05 level). All efficacy analyses were based on end-of-treatment efficacy patients who had no clinically significant protocol violations and a minimum of 3 months of treatment.

Results

Demographics: The two groups were fairly well matched for baseline characteristics. The mean age was 31 years, 85% of the patients were Caucasian, 5% Black, and 5% Hispanic. Of note, 37% of nafarelin vs. 18% of leuprolide subjects were current smokers ($p=0.002$) (the baseline BMD in the nafarelin smokers vs. nonsmokers was 1.14 vs. 1.16; and in the leuprolide patients: 1.15 vs. 1.15).

Disposition: (See flow diagram) A total of 236 subjects were enrolled by 20 investigators. Of these subjects, 208 received study drug and were included in the safety analyses. One hundred ninety-two patients were included in the efficacy analyses (99 in nafarelin and 93 in leuprolide). Sixteen women were excluded: one because she received both drugs; one because she had previous HRT without a 30-day washout; and 14 because they received less than 3 months of treatment.

Nineteen percent (40) of the subjects discontinued from the study prematurely for the reasons shown in the accompanying flow diagram.

Endometriosis: 88% of nafarelin subjects vs. 90% of leuprolide patients had improvement in the total sign and symptom severity score at the end of active treatment (lower bound of 95% CI = -11%; $p < 0.001$). 35% of nafarelin vs. 40% of leuprolide patients had improvement in the total sign and symptom severity score at the end of the post-treatment follow-up period (lower bound of 95% CI = -17%; $p = 0.02$).

Estradiol Levels: In a subset of patients, the median baseline estradiol levels were significantly higher in the leuprolide vs. the nafarelin subjects: approximately 70 pg/ml in 20 nafarelin patients and about 140 pg/ml in 22 leuprolide subjects. During the treatment phase the nafarelin participants had consistently higher median serum estradiol levels than those in the leuprolide group: nafarelin, range: 12-20 pg/ml and leuprolide, range: 8-12.5 pg/ml. At Month 6, however, the mean and median estradiol levels were higher in the nafarelin patients compared with the leuprolide subjects: mean: 25 vs. 19 pg/ml and median: 15 vs. 10 pg/ml; $p = 0.5$.

Bone Mineral Density: The mean baseline BMD values were comparable for the two groups: 1.15 vs 1.14: nafarelin and leuprolide, respectively ($p = 0.7$). The mean percent changes in BMD from baseline to end of treatment were -3.2% and -4.5% for the nafarelin and leuprolide subjects, respectively ($p = 0.002$). The mean percent changes in BMD from end of treatment to 6 months post-treatment were -1.5% and -2.5% for the nafarelin and leuprolide groups, respectively ($p = 0.07$). The results of the analyses were similar when the patients without bone density correction factors were excluded and when age was introduced as a covariate. In an intent-to-treat analysis of 177 patients, including protocol violators, the mean percent change in BMD from baseline to end of treatment was -3.0% in the nafarelin group and -4.6% in the leuprolide group. $p < 0.001$. Parenthetically, the company states that no interpolations or extrapolations were performed to replace any missing data.

MEDICAL OFFICER'S COMMENTS

The data from this study indicate that BMD decreased to a lesser degree following 6 months of treatment with 400 ug/day of nafarelin compared with 3.75 mg/month of leuprolide in women with endometriosis. Data from a subset of women suggest that the changes in BMD may have been due to a greater reduction in estradiol levels in the women receiving leuprolide compared with nafarelin.

Based on the data submitted and reviewed I recommend the following changes (shown in bold) be made to the labeling in the Clinical Pharmacology section.

Patients on both treatments experienced bone mineral density (BMD) loss as assessed by L1-L4 dual x-ray bone densitometry (DEXA).

ISI

11/4/98

Eric Colman, MD

11/3/98

Cc: HFD-510 Consult File
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Orig NDA 19-886

HFD-580/div. file

11/4/98

FLOW DIAGRAM

Active Treatment Phase

	Nafarelin	Leuprolide
Enrolled	118	118
Received Drug	105	103
D/Cd early	15	25
Efficacy Analyses	99	93
Completed 6 Months	90	78

Reasons for Termination

AE	7	13
Ineffective Tx	3	3
LTF	0	5
Non-compliance	2	0
Death	1	0
Other	2	4

Post-Treatment Follow-up

	Nafarelin	Leuprolide
Enrolled	90	78
D/Cd early	32	19
Completed 12-month Study	58	59

SAFETY UPDATE FOR SYNAREL (~~NAFARELIN~~ ACETATE)

Document Number: N6S-98-07-922
Document Date: 18 December 1998
Authors: Gail Gersh, R.N., Ph.D.
Michael C. Snabes, M.D., Ph.D

Nafarelin Acetate
Safety Update for Synarel

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NGS-98-07-922
18 Dec 1998

APPROVAL/SIGNATURE(S)

/S/

12.18.98

Michael C. Smabes, M.D., Ph.D.
Associate Director
Clinical Research

Date

SAFETY STATEMENT

All information has been reported. There is no additional clinical information to report. In addition, there have been no Post Marketing Reports that would require a label change.

APPEARS THIS WAY
ON ORIGINAL