CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19726/S22

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19-726/S-022

Food and Drug Administration
Rockville MD 20857

APR 09 1998

Zeneca Pharmaceuticals Inc.
Attention: Ms. Kimi DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

Dear Ms. DeNoble:

Please refer to your supplemental new drug application dated April 8, 1997, received April 9, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoladex (goserelin acetate implant) 3.6 mg.

We acknowledge receipt of your submissions dated June 6, July 3, September 26, and December 8, 1997; February 12, April 2, 3(2) and 8, 1998. The User Fee goal date for this application is April 9, 1998.

The supplemental application provides for an addition to the PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINSTRATIONS sections regarding the use of hormone replacement therapy in reducing the bone mineral density loss associated with the use of Zoladex alone for the treatment of endometrosis.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated April 3, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on April 3, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-726/S-022. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Alvis Dunson, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S22

MEDICAL REVIEW(S)

SAFRAN

MAR 9 1998

Addendum to Medical Review
NDA 19-726/S-022

In a labeling meeting held March 9,1998 it was decided that none of the labeling changes requested by the sponsor be accepted. The following two sentences will be added to the end of Changes in Bone Mineral Density in the Adverse Reaction Section and added to the end of section 5 on bone mineral density in the Warning section:

The optimal drugs, dose and duration of treatment has not been established.

/S/

Julian Safran M.D.
Medical Officer HFD-580

cc. NDA-19-726/Division File/ADunson/LRarick/ /JSafran

Agree
3/9/98

MEDICAL REVIEW
NDA 19-726/S-022

MAR 9

1. **Resume**

This supplemental NDA, based on a study done without an IND and apparently without prior discussion with the Agency, is a proposal to add to the Clinical Studies section, and other sections, of the label, reference to findings which appear to demonstrate that two hormone replacement ("HRT") regimes, when used with the subject drug given for endometriosis, act equally effectively to counteract the osteoporotic effects and menopausal symptoms induced by the subject drug, without reducing its favorable effects. This reviewer recommends that the use of various forms of "add-back" therapy which, though not approved under NDAs, have entered clinical practice, be acknowledged in the label, but that the Agency not endorse the specific regimen employed in this study by permitting it to be cited in the label.

2. **General information**

2.1. **Medical Officer's review**

2.1.1. **NDA:** 19,726/S-022

2.1.2. **Submission received:** 9 April 1997

2.1.4. **Review submitted:** 17 December 1997

2.2 **Drug names**

2.2.1. **Generic name:**
Goserelin acetate implant

2.2.2. **Trade name:**
Zoladex

2.3 **Sponsor:**
Zeneca Pharmaceuticals
Wilmington DE

2.4 **Pharmacological category:**
Long acting gonadotropin-releasing hormone agonist

2.5 **Approved indications**

2.5.1. Prostatic carcinoma

2.5.2. Endometriosis
[This supplement relates only to labeling for the endometriosis indication.]

2.5.3. Advanced breast cancer

2.6. **NDA drug classification:** S

2.7. **Related drugs**
Other drugs in this class include **leuprolide acetate** (approved for the treatment of

endometriosis, leiomyomata uteri, prostatic cancer, and precocious puberty), **nafarelin acetate** (approved for endometriosis and precocious puberty), and **histrelin acetate** (approved for precocious puberty).
[**NOTE**: to date labeling for the endometriosis indication warns against use for more than 6 months.]

3. **Chemistry/manufacturing controls**
Not relevant to this Supplement.

4. **Animal Pharmacology/Toxicology**
Not relevant to this Supplement.

5. **Human Pharmacology, Pharmacokinetics, Pharmacodynamics**
Not relevant to this Supplement.

6. **Biometrics**
See the Biometrics review for a comprehensive discussion of the statistical aspects of the study.

7. **Material reviewed, including relevant journal articles which are listed in chronological order, and *for which brief synopses of findings are provided***

7.1. The subject NDA.

7.2. NDA 20-011/S-012
NDA 20-011
NDA 20-708/Efficacy supplement
Supplements to NDAs 20-011 and 20-708 are applications from TAP Holdings Inc. requesting label changes for their 1 month and 3 month forms of leuprolide to include description of another regimen of "add-back" therapy, in this instance composed of norethindrone (NET) alone.

7.3. Paterson ML.(1982) A randomized double-blind cross-over trial into the effect of norethisterone on climacteric symptoms and biochemical profiles. Br J Obstet Gynaecol 89:464-72.
This cross-over study in 23 women for 3 months demonstrated that norethisterone (NET) 5 mg/d provided relief from vasomotor symptoms.

7.4. Madel FP et al.(1982) Effects of progestins on bone metabolism in postmenopausal women. J Repro Med 27(sup):511-14.

Medroxyprogesterone acetate 20 mg/d given to 10 subjects for 4 weeks had a beneficial effect on Ca/Cr and OHPr/Cr levels, but less that the beneficial effect of ethinyl estradiol.

7.5. Riis BJ et al.(1990) Is it possible to prevent bone loss in young women treated with luteinizing hormone-releasing hormone agonists? J Clin End Metabol 70:920-24.
In a study of women on intranasal nafarelin given for endometriosis, it was concluded that the 15 women who completed 6 months on additional NET 1.2 mg/d experienced a "bone-sparing effect".

7.6. Surrey ES et al.(1990) The effects of combining norethindrone with a gonadotropin-releasing hormone agonist in the treatment of symptomatic endometriosis. Fertil Steril 53:620-6
Ten patients given histrelin for endometriosis experienced relief of vasomotor symptoms and bone-sparing when given titrated doses of NET, beginning at 0.35 mg/d to a maximum of 3.5 mg/d for 24 weeks.

7.7. Lemay A, Surrey ES, Friedman AJ.(1992) Extending the use of gonadotropin-releasing hormone agonists: the emerging role of steroidal and nonsteroidal agents. Fertil Steril 61:21-33.
This review article discusses studies to date with continuous progestogen add-back for endometriosis and other gynecological conditions, and concludes that "although the precise use of long-term GnRh-a therapy (in conjumction with sex steroid add-back therapy) remains unknown, the information provided strongly supports additional studies in the area.." (emphasis added)

7.8. Judd HL.(1992) Gonadotropin-releasing hormone agonists: strategies for managing the hypoestrogenic effects of therapy. Am J Obstet Gynecol 166:752-6
The author reviews add-back with MPA and NET for women receiving GnRh-a for endometriosis and notes that "my recommendation is to add NET 2.5 mg daily.."

7.9. Barbieri RL.(1992) Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol 166:740-5.
In this theoretical discussion of the discrimination that must be made between endometriotic symptoms and bone sparing, the author postulates that there is a "therapeutic window" of 30-50 pg/mL estrogen that should be the goal of effective and safe treatment. He concludes: "a major question that is still unresolved is: <u>What precise concentration of estradiol is required to produce atrophy of endometriotic lesions</u>?" (emphasis added)

7.10. Friedman AJ, Hornstein MD.(1993) Gonadotropin-releasing hormone agonist plus estrogen-progestin "add-back" therapy for endometriosis-related pelvic pain. Fertil Sterl 60:236-40.
Six women given leuprolide for endometriosis had no apparent bone loss and lower pelvic pain scores when given Premarin 0.625 mg/d and MPA 2.5 mg/d for the last 21 months of a 2 year study.

7.11. Adashi EY.(1994) Long-term gonadotrophin-releasing hormone agonist therapy: the evolving issue of steroid 'add-back' paradigms. Human Reproduction Update 9:1380-97.
In this extensively referenced monograph of "add-back" therapy, the author notes that in order to avoid the use of estrogen in "add-back" (and thus avoid estrogen's possibily stimulatory effects on the endometrium) most studies thus far have employed progestins alone; only 2 studies of HRT are referenced: a case report and Friedman and Hornstein (7.10.). The author concludes: "<u>Substantial additional studies would have to be carried out to validate the utility of steroid 'add-back' regimens. ..The concurrent or non-concurrent use of non-steroid 'add-back' regimens will also most likely constitute a major component of future studies</u>". (emphasis added) [NOTE: see Appendix 1 for a copy of this useful review.]

7.12. Surrey ES.(1995) Steroidal and nonsteroidal "add-back" therapy: extending safety and efficacy of gonadotropin-releasing hormone agonists in the gynecological patient. Fert Steril 64:673-85.
In this review, the author notes, as does Adashi(7.11.), that experience with HRT as add-back in endometriosis is very limited. He concludes: "No single add-back regimen is appropriate for all gynecological indications for GnRH-a".

7.13. Surrey ES et al.(1995) Prolonged gonadotropin-releasing hormone agonist treatment of symptomatic endometriosis: the role of cyclic sodium etridronate and low-dose norethindrone "add-back" therapy. Fertil Steril 63:747-55.
Of 19 women with endometriosis treated with leuprolide, 10 received etridronate 400 mg/d plus NET 2.5 mg/d and 9 received NET 10 mg/d alone for 48 weeks. Both groups experienced no bone loss or vasomotor symptoms, although the NET alone group experienced adverse blood lipid levels.

7.14. Howell R et al.(1995) Gonadotropin-releasing hormone analogue (goserelin) plus hormone replacement therapy for the treatment of endometriosis: a randomized controlled trial. Fertil Steril 64:474-481.
This randomized trial of 50 women with endometriosis receiving goserelin comparing placebo with transdermal estrogen plus MPA indicated that this HRT "add-back" regimen was beneficial except that bone loss at the lumbar spine "was not prevented completely".

7.14. Kiilholma P et al.(1995) Comparison of the gonadotropin-releasing hormone agonist goserelin acetate alone versus goserelin combined with estrogen-progestogen add-back therapy in the treatment of endometriosis. Fertil Steril 64:903-8.
This double-blind placebo-controlled 12 month study in 76 women demonstrated that 17 beta-E2 ("Kliogest") 2 mg/d plus norethisterone 1 mg/d "did not reduce the efficacy of goserelin but diminished the postmenopausal symptoms during

treatment". Bone density measurements were not made.

7.15. Edmonds DK.(1996) Add-back therapy in the treatment of endometriosis: the European experience. Br J Obstet Gynaecol 103(sup):10-13.
The author reviewed 2 placebo-controlled studies of add-back in women receiving goserelin. One study involved 25 women on 25 mgm estradiol patches plus MPA 5 mg/d; the other study is the one cited in 7.14. These studies suggested that both "add-back" regimens were effective.

7.16. Moghissi KS.(1996) Add-back therapy in the treatment of endometriosis: the North American experience. Br J Obstet Gynaecol 103(sup):14
This one page article is a brief summary of the study which is the subject of this review.

8. Review of "add-back" therapy for the treatment of endometriosis

The term "add-back" was coined to identify a variety of drugs used to counter the vasomotor symptoms and bone loss induced by GnRH-a drugs. To date, GnRH-a drugs are only approved in gynecological practice for endometriosis and fibroids, as noted in 2.7. Agonists are also used "off-label" for other gynecological conditions such as the premenstrual syndrome, dysfunctional uterine bleeding, and infertility.

At present, labeling states that the fibroid indication is limited to pre-operative use to ameliorate the anemia often associated with this condition whereas labeling for endometriosis limits the use of the agonist to 6 months because of the bone loss associated with its use. It seems clear that an ultimate additional goal of "add-back" therapy is to extend the length of time the agonist may be given; the literature on this subject is replete with the notion that "endometriosis is not a 6 month disease". This is certainly true, but, nevertheless, the restriction of agonist use to 6 months is in place for important safety concerns, and any effort to extend the period of exposure must be approached with caution. [**NOTE**: Another sponsor attempted to extend the treatment period to 12 months with a specific "add-back" regimen, but the request was denied.(Cf.NDA 20-011/S-012)].

To date **three forms of "add-back" therapy** have been employed in the treatment of endometriosis:

8.1. **Progestins alone**

As noted in the literature review, most experience to date with "add-back" has been with progestins alone rather than with "HRT", following the notion that giving estrogens might counter the favorable effect of the GnRH-a on the disease. Also, progestins may inhibit endometrial growth, and thus may have a therapeutic effect on the endometriotic lesions.

In his review, Adashi describes a total of 4 studies to date using progestins alone as "add-back", involving 55 subjects given different GnRH-a drugs and different progestins at different doses (see Table VII on page 1387 in Appendix 1). Adashi states that "(a)lthough a larger number of patients would be required to confirm the preceding observations, the preliminary data available would suggest that appropriately-tailored progestin 'add-back' therapy may well prove protective..." [**NOTE**: A larger study, as yet unpublished, of NET 5 mg/d as "add-back", is the subject of NDAs 20-011 and 20-708.]

8.2. **"Hormone Replacement Therapy" (HRT)**

Experience with combined estrogen-progestin therapy, also known as "HRT", as "add-back" is even more limited. Early in this decade investigators followed the lead of Barbieri, then at Harvard, who proposed the "estrogen threshold hypothesis", the details of which are provided in reference 7.9. Barbieri postulated that a blood level of 30-50 pg/mL estrogen is the "therapeutic window" that should provide the appropriate balance between endometriosis symptoms and bone sparing.

Reid reported one case in 1992 of a women on goserelin who was given an "HRT" regimen as "add-back", and Friedman and Hornstein (7.10.) reported 8 women on histerelin for endometriosis given an "HRT" regimen as "add-back". The "HRT" regimen employed was conjugated estrogens 0.625 mg/d plus MPA 2.5 mg/d. All subjects were reported to experience reduced vasomotor symptoms and no bone loss.

The only other study of conjugated estrogens plus MPA as "add-back" is the subject of this review but the doses differ from those cited above.

8.3. **Etridronate**

To date there appears to be only one published study suggesting that etridronate may be a suitable choice for "add-back" therapy, because of its bone sparing effects(7.13.). [**NOTE**: It's also possible that now that raloxifene may be approved for treatment of osteoporosis, that attempts to use it and related drugs for "add-back" therapy will be attempted.]

One concludes from this review that **to date an optimal "add-back" regimen has not been found for women being treated with GnRH-a drugs for endometriosis**. This conclusion is in concurrence with those of Adashi(7.11.) and Surrey(7.12.).

9. **Review of the submitted study**

INTRODUCTION

This study, descriptively entitled "**A Multicenter Trial Comparing 3.6-mg ZOLADEX Therapy With or Without Hormone Replacement Therapy for the Treatment of Endometriosis**", was a randomized, double-blinded, trial with 3 arms (0.3 mg Premarin + 5 mg Provera, 0.625 mg Premarin + 5 mg Provera, and placebo) and was designed to ascertain the ability of two HRT regimes to ameliorate the bone loss and menopausal symptoms induced by Zoladex given for the treatment of endometriosis, without reducing the efficacy of the treatment. The treatment period was 24 weeks, with a follow-up period of 48 weeks. The study, which included 345 subjects and was conducted in 42 centers in this country and Canada, was completed in September 1995, and has been presented at medical meetings(7.16.).

The study was done without an IND and the Program Manager responsible for this submission reported no documented discussions with the Agency concerning the study prior to the submission of the NDA.

The sponsor's summary, provided in **Appendix 2** (NDA Volume 2, pages 19-24), indicates appropriate inclusion and exclusion criteria, correct blinding procedures,

adequate clinical monitoring, and, apparently correct statistical calculations, although the review by the Biometrics Team must be considered in this regard. Therefore details concerning these aspects of the study will not be repeated here. However the endpoints and their implications for whether the study should be cited in labeling require comment.

ENDPOINTS

As noted in NDA Volume 2, page 39, "the **primary efficacy endpoint** for this trial was relief of pain as measured by absolute change in **total pelvic symptom score** and **total subjective symptom score**. The "**secondary efficacy end points ... were percentage change in BMD** and **physiological side effects**".

The **total pelvic symptom score** was "the sum of the scores for dysmenorrhea, dyspareunia, and pelvic pain", all of which were rated periodically by the subjects.(page 39) The **total subjective symptom score** was "the sum of the scores included in total pelvic symptom score plus the two additional symptoms scores for pelvic tenderness and pelvic induration"(page 40), obtained at the time of pelvic examinations. The **percentage change in BMD** requires no further definition, and the **physiological side effects**, also called "physiological symptoms"(page 41), "included vaginal dryness, depression, mood swings, headache, and hot flashes (vasodilation)", each rated periodically by the subjects.

Though not designated one of the endpoints, "menstrual bleeding measurements" were also taken.

OUTCOMES

Refer to the summarizing **Figures**, taken from pages between page 49 and 74 of NDA Volume 2, provided in **Appendix 3**.

Figure 1 demonstrates that the **total pelvic symptom scores** for the entire 72 weeks of the study show almost exact concurrence for the 3 study groups for the 72 week study period. [**NOTE**: HRT0=placebo; HRT1 = Premarin 0.3 mg + Provera 5 mg; HRT2 = Premarin 0.625 mg + Provera 5 mg] **Figure 2** demonstrates a similar concurrence of effects for the **total subjective symptom score**.

Although the scores are admittedly arbitrary, they appear sufficiently to reflect clinical experience to warrant the conclusion that these 2 forms of "add-back" therapy do not appear to inhibit the pain-relieving effects of the agonist.

Figure 3 displays the **mean bone mineral density** scores for the three groups for the 72 week period. The placebo group's density fell significantly at the end of the treatment period, whereas both treatment groups prevented bone loss, **although not completely**. All subjects received the agonist during the 24 week treatment period.

The 6 graphs in **Figure 4** display various physiological effects of the 3 regimens. It appears that all 3 regimens had similar effects on "Depression", "Mood Swings", and "Headache", whereas both "HRT" regimens were equally effective in relieving "Hot flashes", **although not completely**. "Vaginal dryness" is the only symptom in which the higher Premarin dose "HRT" was more effective that the lower dose.

Figure 5, showing the estradiol levels at each visit, is included out of interest because of Barbieri's postulation that the goal of "add-back" therapy should be to achieve estradiol levels between 30 and 50 pg/L. The findings of this study are that the placebo group's estradiol level during treatment was about 20 pg/L, the lower Premarin dose group was about 50 pg/L, and the higher Premarin dose group was about 100 pg/L.

Figure 6 shows 3 characteristics of vaginal bleeding during the study. All 3 drug groups were equal in their suppression of "average flow days" and "heavy flow days", but the "number of days of spotting" varied during the treatment period, with more spotting in the higher Premarin dose group.

DEFICIENCIES

Although, as noted above, these two "HRT" regimens appear to alleviate at least some of the vasomotor symptoms and bone loss inducted by a GnRH-a drug when given for endometriosis without nullifying the favorable effect of the agonist on the pain of the disease, the following deficiencies exist in the current study:

- Only one study was done; as a rule, 2 pivotal studies are required for approval.

- Neither "HRT" regimen used in this study is approved for prevention of vasomotor symptoms and bone loss in menopausal women. (Furthermore, as argued in 10, it would not be acceptable to extrapolate findings from the use of an "HRT" regimen approved for use in menopausal women to the use of the same regimen when used as "add-back" in younger women. Therefore, use of an approved "HRT" regimen as "add-back" would not be an argument for including reference to it in the label.)

- There was no dose-finding.

- Since both doses of "HRT" were found essentially equivalently effective, permitting this specific study to appear in labeling would not provide satisfactory guidance to clinicians and patients.

10. **Conclusions concerning the request to include the specific study in labeling**

The findings cited in Sections 7 and 9 support the widely-held clinical impression that various forms of "add-back" therapy may be a useful adjuvant to the use of GnRH agonists in women. Therefore it seems acceptable to mention in the label the apparent benefits of "add-back" therapy in general terms, but it would not be acceptable to cite this specific study for the following reasons:

"Add-back" therapy is not sufficiently understood for the Agency to approve a specific regimen. Even though the term "add-back" appears to have become accepted in gynecological practice, the literature review cited above makes it clear that this is an essentially new and poorly understood modality. There is no consensus concerning appropriate drugs and doses.

This reviewer finds the term "add-back" therapy suspect because the term implies that the treatment will result in reestablishment of normal conditions made abnormal by the agonist. Actually, as noted above, the vasomotor symptoms and bone loss were not maintained completely at pretreatment levels by either "add-back" regimen.

Furthermore, it must be noted that it is an error to extrapolate what is known about providing an "HRT" regimen to menopausal women to what is not yet known about giving "add-back" to young women on GnRH-a drugs. More research is certainly required. For example, this study is similar to other studies of "add-back" regimens

in failing to give adequate attention to such safety issues as the effects of the drug combinations on blood lipids and clotting factors, surrogates of cardiovascular disease.

Several years ago, in response to clinical practice, the Agency added to the estrogen label the statement that "studies of the addition of a progestin for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia". However, a specific regimen of "HRT" wasn't mentioned in labeling until a sponsor undertook appropriate and fully-compliant studies. A similar, more deliberate approach, is desirable for "add-back" therapy.

Permitting the study to be cited in the label would allow the sponsor to promote the use of this specific regimen when, as argued above, there is insufficient information on the use of "add-back" therapy for the Agency to approve any specific regimen as safe and effective. Such approval would provide unwarranted confidence to clinicians and would raise the likelihood that meaningful research in this important field would be inhibited.

A larger problem relates to the extensive promotion of "HRT" therapy currently underway by sponsors and clinicians. If the use of this specific regimen were to become codified into practice through its inclusion in the label, and if in time sponsors were successful in extending the use of GnRH-a beyond 6 months, one may expect that many women might be exposed to "HRT" for a significant portion of their life-span, with, as yet, unknown effects.

Finally, adding this specific regimen to the label would be further complicated if other "add-back" regimens were to be added to labels of other GnRH-a drugs. This will occur if supplements to NDAs 20-011 and 20-708, in which the sponsor requests providing details of a norethindrone-only "add-back" regimen to the leuprolide label, are approved as requested.

11. **Review of the labeling**

For the reasons cited in section 10 of this review, it is suggested that none of the label changes requested by the sponsor be accepted, but that the following 2 sentences be added to the end of **Changes in Bone Mineral Density** in the **ADVERSE REACTIONS SECTION:**

Many clinicians believe that the use of so-called "add-back" therapy, composed of different steroidal and non-steroidal drugs given at different doses, reduces the vasomotor symptoms and bone loss associated with the administration of GnRH agonists without diminishing the favorable effects for which the agonists are given. Nevertheless, clarification of the definition of "add-back" therapy is necessary and the optimal drugs, doses, and duration of treatment have not been established.

12. **Recommendations**

12.1. It is recommended that the submission be approved, but that the label change be limited as specified.

12.2. It might be useful to seek the advice of the Division"s Advisory Committee on this important clinical issue and to develop guidance for sponsors interested in "add-back" therapy.

/S/

Philip A. Corfman, MD
Medical Reviewer

cc: IND/NDA Arch
HFD-580/Rarick/~~Jelson~~/Corfman//wpfiles\19726.nda

We will proceed with general labeling statements in the Warnings and Adverse Event section as per 3/7/97 no addendum.

/S/

3/7/97

Human Reproduction Update vol.9 no.7 pp.1380–1397, 1994

Attachment 1.1.

Long-term gonadotrophin-releasing hormone agonist therapy: the evolving issue of steroidal 'add-back' ıdigms

Eli Y.Adashi

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, The University of Maryland School of Medicine, 405 West Redwood Street, 3rd Floor, Baltimore, MD 21201, USA

The introduction of steroid 'add-back' regimens draws on the recognition that several clinical entities targeted for treatment with gonadotrophin-releasing hormone agonist (GnRHa) are not '6-month diseases'. Included under this heading are individuals suffering from symptomatic endometriosis (not desires of pregnancy), uterine fibroids (ineligible or disinterested in definitive surgical therapy), ovarian hyperandrogenism, premenstrual syndrome, menopausal transition, or dysfunctional uterine bleeding. A 6-month course of therapy with a GnRHa does not adversely affect lipoprotein economy and therefore presumably the corresponding cardiovascular risk. A 6-month course of GnRHa therapy appears to be associated with a substantial e (of up to 8.2%) in lumbar bone density, a p. .nenon which may not be entirely reversible 6 months after discontinuation of therapy. In principle, steroid 'add-back' therapy should diminish some or all of the side-effects associated with GnRHa therapy, may provide a medical treatment option for patients representing a high surgical risk, and may delay surgical intervention if desired. On the other hand, a steroid 'add-back' therapy may delay tissue diagnosis, be associated with a substantial cost as well as with the need for parenteral route of administration. Norethindrone-only (but not medroxyprogesterone acetate-only) 'add-back' regimens have proved promising in the context of endometriosis. Non-concurrent oestrogen/progestin 'add-back' regimens proved promising in the context of uterine fibroids. Substantial additional studies would have to be carried out to validate the utility of steroid 'add-back' regimens. Special emphasis will have to be placed on the evaluation of long-term utility with an eye towards assessing clinical efficacy, impact on lipoprotein economy, impact on bone density, impact on urogenital tissues, and impact on the hot flush. The concurrent or non-concurrent use of non-steroid 'add-back' regimens will also most likely constitute a major component of future studies.

K ords: add-back paradigms/gonadotrophin-releasing

Introduction

There is little doubt that the introduction of gonadotrophin-releasing hormone agonists (GnRHa) has all but revolutionized the practice of reproductive endocrinology (Sandow, 1983; Yen, 1983; Cutler *et al.*, 1985; McLachlan *et al.*, 1986; Andreyko *et al.*, 1987; Filicori and Flamigni, 1988; Fraser, 1988; Friedman and Barbieri, 1988; Lemay, 1989). In this connection, special mention must be made of the highly successful short-term (up to 4 weeks) application of these principles in the context of assisted reproductive technology (MacLachlan *et al.*, 1989). Equally important however is the application of GnRHa under circumstances calling for their longer-term application. In this connection, special consideration must be given to the already established salutary effects of these principles when applied for up to 6 months to the management of endometriosis (Meldrum *et al.*, 1982, 1983; Lemay and Quesnel, 1982; Shaw *et al.*, 1983, 1992a,b; Pring *et al.*, 1983; Lemay *et al.*, 1984, 1988; Schriock *et al.*, 1985; Hardt *et al.*, 1986; Zorn *et al.*, 1986; Jelley, 1987; Steingold *et al.*, 1987; Matta and Shaw, 1987; Shaw, 1988, 1991; Henzl, 1988, 1989; Henzl *et al.*, 1988; Dmowski *et al.*, 1989; Tummon, 1989; Dlugi *et al.*, 1990; Barbieri, 1990a; Wheeler *et al.*, 1992, 1993; Rock *et al.*, 1993), uterine fibroids (Filicori *et al.*, 1983; Maheux *et al.*, 1984, 1985, 1987; Healy *et al.*, 1986; Maheux, 1986, Coddington *et al.*, 1986; Friedman *et al.*, 1987, 1989a,b, 1991; Lumsden *et al.*, 1987; West *et al.*, 1987; Kessel *et al.*, 1988a,b; Matta *et al.*, 1988a,b, 1989; Andreyko *et al.*, 1988; Benagiano *et al.*, 1988; Bianchi and Fedele, 1989; Schlaff *et al.*, 1989; Letterie *et al.*, 1989; Vollenhoven *et al.*, 1990; Stoval *et al.*, 1991; Adamson, 1992; Watanabe *et al.*, 1992), or precocious puberty (Crowley *et al.*, 1981; Mansfield *et al.*, 1983; Luder *et al.*, 1984; Styne *et al.*, 1985; Stanhope *et al.*, 1985; Comite *et al.*, 1985). It is in these contexts that the unique ability of GnRHa to put the reproductive axis at rest, at will, for the duration of the therapy is being put to good use.

The above notwithstanding, current therapeutic regimens involving the use of GnRHa must be viewed as restrictive in terms of the permissible duration of application. Indeed, with the exception of the indication of precocious puberty, use of GnRHa in the context of reproductive endocrine disorders (e.g., endometriosis or uterine fibroids) is limited to 6 months in duration. Understandably, this latter limit was prompted by concerns relevant to the possibility that longer-term application of GnRHa may result in profound and potentially irreversible

bone loss not to mention other consequences of the hypo-oestrogenic state which inevitably ensues. Fortunately for subjects afflicted with endometriosis-associated infertility, a 6-month therapeutic regimen may (at times) be all that is required for the genesis of a temporary yet indispensable fertile time window. Not so, however, is the case for subjects presenting with symptomatic endometriosis whose concerns are of a longer-term nature and whose management may require an open-ended approach. Similar considerations apply to select subjects afflicted with symptomatic uterine fibroids for whom a surgical option must be ruled out. Clearly then, specific therapeutic needs raised by day to day clinical practice requirements may not be satisfactorily met by current therapeutic strategies. If nothing else, it is this line of reasoning which recognizes the fact that many of the disease states targeted for treatment with GnRHa are not '6-month diseases'. Indeed, should GnRHa be applied in the context of chronic afflictions such as ovarian hyperandrogenism, the menopausal transition, or the premenstrual syndrome, longer-term application strategies would inevitably have to be devised. Undoubtedly, the long-term provision of GnRHa by itself would constitute an unreasonable therapeutic proposition, given the inevitable consequences of the long-term hypo-oestrogenic state. It is precisely this therapeutic challenge which underlies the rationale for steroid 'add-back' therapy to which this review is dedicated.

On the surface at least, chronic applications of GnRHa could have been made possible by adjunctive oestrogen replacement therapy. However, as intuitive reasoning would clearly indicate, such a therapeutic manoeuvre could (in the context of oestrogen-dependent pathology) run the risk of undermining the very purpose of the treatment designed to achieve the therapeutic hypo-oestrogenic state required. Exceptions to this line of reasoning may include several therapeutic indications such as the example of ovarian hyperandrogenism, an androgen- rather than an oestrogen-dependent state wherein no contra-indication exists *a priori* for sex steroid replacement. On the contrary, the concurrent provision of oestrogen/progestin replacement therapy may well prove of therapeutic benefit in this context. In most other circumstances, however, careful evaluation must be undertaken of the feasibility and utility of 'steroid add-back' in the context of oestrogen-dependent disease states.

It is the purpose of this communication to critically review the current status of GnRHa/steroid 'add-back' regimens in an effort to assess the prospects of such a therapeutic strategy. Admittedly, efforts along these lines may well be viewed as naive and as attempting to 'have one's cake and eat it too'. However, serious consideration must be given to the prospect that adjunctive steroid replacement therapy could be safely provided against the backdrop of long-term GnRHa application in the best interest of those clinical conditions currently beyond the reach of contemporary GnRHa therapy.

Why steroid 'add-back' therapy?

As might be expected, the response to the above query would appear self-evident. Indeed, the question might well be viewed as rhetoric in that the rationale for steroid 'add-back' therapy in the context of long-term GnRHa application would inevitably be to combat the consequences of the GnRHa-induced hypo-oestrogenic state. In this connection, a series of well-defined consequences, not unlike those experienced in the climacteric would have to be addressed. For example, issues of quality of life, i.e., the occurrence of urogenital atrophy and of hot flushes are clearly in need of effective redress. More importantly however, consideration must be given to the attenuation and possibly virtual elimination of the more serious (and potentially life-threatening) consequences of the hypo-oestrogenic state, i.e., increased bone loss and decreased cardioprotection. Indeed, it is these latter complications which affect the quantity rather than the quality of life.

In attempting to define the issues at hand, the key question which must be answered has to do with the feasibility of the design of 'add-back' regimens which would allow the long-term application of GnRHa. Moreover, efforts must be directed at establishing whether it is possible to diminish the adverse side effects associated with GnRHa therapy without compromising therapeutic efficacy.

GnRHa-induced cardiovascular risks

Despite the central importance of cardiovascular parameters to long-term GnRHa application, relatively little information is available to address this issue at this time. Indeed, heavy reliance must be made on studies wherein GnRH agonists were applied for a total of 6 months in keeping with current guidelines (Lemay, 1989; Henzl *et al.*, 1988; Cirkel *et al.*, 1988; Burry *et al.*, 1989; Valimaki *et al.*, 1989; Crook *et al.*, 1989; Bergquist, 1990;

Table I. Effect of gonadotrophin-releasing hormone agonist (GnRHa) on the lipoprotein pattern

Authors	Year	Subject (#)	Analogue	Low-density lipoprotein	High-density lipoprotein
Henzl	1988	156	Nafarelin	–	↑
Burry *et al.*	1989	35	Nafarelin	–	–
Cirkel *et al.*	1988	64	Buserelin	–	↑
Valimaki *et al.*	1989	12	Nafarelin	–	↑
Lemay	1989	32	Buserelin/ goserelin	–	–
Crook *et al.*	1989	21	Goserelin	–	–
Bergquist	1990	15	Nafarelin	–	–
Surrey and Judd	1992	10	Leuprolide	–	–
Wheeler *et al.**	1993	134	Leuprolide	–	–

*Up to 13% of patients did display an increase or decrease in lipoprotein levels.

Attachment 1.3.

Surrey and Judd, 1992; Riis *et al.*, 1990). Unfortunately, even that database proves relatively limited, the overall literature experienced thus far totalling 479 subjects (Table I). Inevitably, no information is available at this time with respect to actual GnRHa-associated cardiovascular events. Rather, heavy use is being made of the predictive value of the circulating lipoprotein pattern. Given this parameter, the literature appears highly uniform in documenting the fact that the provision of GnRHa for a total of 6 months is without a measurable adverse effect on the lipoprotein pattern as assessed in terms of the circulating concentrations of low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Indeed, whereas the circulating concentrations of LDL proved invariably unchanged [with one exception (Riis *et al.*, 1990)], the circulating concentrations of HDL were judged to be stable (Lemay, 1989; Burry *et al.*, 1989; Crook *et al.*, 1989; Bergquist, 1990; Surrey and Judd, 1992, Riis *et al.*, 1990) or increased (Henzl *et al.*, 1988; Cirkel *et al.*, 1988; Valimaki *et al.*, 1989). As such, these findings would suggest a short-term (6-month) lipid-neutral effect of GnRHa with a possible slight net gain as gauged by the circulating concentrations of HDL.

It goes without saying that the preceding observations provide relatively little insight concerning the longer-term application of GnRHa. However, common sense alone would dictate that the induction of a long-term hypo-oestrogenic state would in fact result in progressively diminishing cardioprotection as has previously been documented for the menopause (Bush *et al.*, 1983; Stampfer *et al.*, 1985; Matthews *et al.*, 1989; Barrett-Connor *et al.*, 1989). That notwithstanding, it is not inconceivable that the profound differences between naturally occurring menopause and its GnRHa-induced counterpart may in fact produce outcomes not immediately predicted by conventional wisdom drawing on experience from the climacteric hypo-oestrogenic state. Moreover, given that steroid 'add-back' therapy will undoubtedly be required in the context of long-term GnRHa application, it would appear prudent to hold judgement on this all important issue until such time that prospective, controlled, double-blind studies have been completed. Intuitive reasoning alone would suggest that the beneficial effects accrued from the post-menopausal provision of sex steroid therapy may well apply in the context of GnRHa-induced hypo-oestrogenism.

GnRHa-induced bone loss

Despite intense concerns as to the possibility of GnRHa-induced bone loss (Fogelman, 1992; Comite, 1989; Dawood, 1993), relatively little is offered by the literature in this regard (Table II). Indeed, thorough evaluation of the world's English-speaking medical literature yields interpretable information on <900 subjects (Steingold *et al.*, 1987; Surrey and Judd, 1992; Riis *et al.*, 1990; Gudmundsson *et al.*, 1987; Devogelaer *et al.*, 1987; Johansen *et al.*, 1988; Matta *et al.*, 1988a; Tummon *et al.*, 1988; van Leusden and Dogterom, 1988; Golan *et al.*, 1989; Damewood *et al.*, 1989; Dawood *et al.*, 1989; Bianchi *et al.*, 1989; Waibel-Treber *et al.*, 1989; Stevenson *et al.*, 1989; Scharla

Table II. Studies on effects of GnRHa on bone economy (n = 840)

Author	Year	No. of Subjects	Diagnosis	Analogue	Dose (ug/day)	Route
Matta and Shaw	1987	13	Endometriosis	Buserelin	1200	IN
Gundmundsson *et al.*	1987	47	Normal	Nafarelin	125/250	IN
Steingold *et al.*	1987a	16	Endometriosis	Histrelin	100	SC
Devogelaer *et al.*	1987	9	Endometriosis	Buserelin	900	IN
Johansen *et al.*	1988	9	Normal	Nafarelin	400	IN
Matta *et al.*	1988a	13	Endometriosis	Buserelin	1200	IN
Tummon *et al.*	1988	25	Endometriosis	Leuprolide/buserelin	1600/1200	IN
Van Leusden and Dogterom	1988	10	Fibroids	Decapeptyl	4000/mo	IM
Golan *et al.*	1989	26	Fibroids	Decepeptyl	3200/mo	IM
Damewood *et al.*	1989	26	Endometriosis/fibroids	Leuprolide	1000	SC
Dawood *et al.*	1989	13	Endometriosis	Buserelin	200–1200	SC/IN
Bianchi *et al.*	1989	18	Fibroids	Buserelin	200	IN
Waibel-Treber *et al.*	1989	18	Endometriosis/fibroids	Decapeptyl	3200/mo	IM
Stevenson *et al.*	1989	11	Endometriosis	Goserelin	3600/mo	SC
Scharla *et al.*	1990	26	Endometriosis/fibroids	Decepeptyl	3200/mo	IM
Whitehouse *et al.*	1990	15	Endometriosis/fibroids	Decapeptyl	3200/mo	IM
Ylikorkala *et al.*	1990	15	Endometriosis	Nafarelin	400	IN
Rittmaster and Thompson	1990	9	Hirsutism	Leuprolide	1000	SC
Dodin *et al.*	1991	17	Endometriosis	Nafarelin	400	IN
Nencioni *et al.*	1991	22	Endometriosis	Goserelin	3600/mo	SC
Surrey and Judd	1992	10	Endometriosis	Leuprolide	3750/mo	IM
Leather *et al.*	1993	20	Premenstrual syndrome	Goserelin	3600/mo	SC
Scialli *et al.*	1993	12	Fibroids	Leuprolide	3750/mo	IM
Wheeler *et al.*	1993	110	Endometriosis	Leuprolide	3750/mo	IM
Rock *et al.*	1993	315	Endometriosis	Goserelin	3600/mo	SC

IN = intranasal; SC = subcutaneous; IM = intramuscular; mo = month.

et al., 1990; Whitehouse *et al.*, 1990; Ylikorkala *et al.*, 1990; Rittmaster and Thompson, 1990; Dodin *et al.*, 1991; Nencioni *et al.*, 1991; Leather *et al.*, 1993; Scialli *et al.*, 1993). The largest series of patients studied involved a total of 315 individuals (Rock *et al.*, 1993). Moreover, the very first relevant reports on this important issue date back only to 1987 (Gudmundsson *et al.*, 1987; Devogelaer *et al.*, 1987). Consequently, despite the fact that GnRHa are being used world-wide by a very substantial number of women, the impact of such therapy on short-term bone loss remains relatively poorly documented. In fact, the information available proves conflicting and puzzling, thereby clearly emphasizing a real need for the execution of large controlled studies in this connection.

The studies available, involving for the most part subjects afflicted with endometriosis or uterine fibroids, made use of different brands of GnRHa applied at variable dose ranges and via different routes (Table II). Consequently, it is reasonable to assume that the overall therapeutic efficacy of the regimens in question varied greatly, particularly with regard to the intensity of the hypo-oestrogenic state which may have been induced. Indeed, it is this very line of reasoning which may well provide the most plausible explanation for the otherwise remarkable disparity documented between individual therapeutic regimens.

In some, but not all cases, specific information is available as to the impact of a 6-month treatment with a GnRHa on bone density (Table III) as assessed at the level of the lumbar spine and the distal radial bone (Surrey and Judd, 1992; Riis *et al.*, 1990; Devogelaer *et al.*, 1987; Johansen *et al.*, 1988; Matta *et al.*, 1988b; Tummon *et al.*, 1988; Golan *et al.*, 1989; Damewood *et al.*, 1989; Dawood *et al.*, 1989; Bianchi *et al.*, 1989; Waibel-Treber *et al.*, 1989; Stevenson *et al.*, 1989; Scharla *et al.*, 1990; Whitehouse *et al.*, 1990; Rittmaster and Thompson, 1990; Dodin *et al.*, 1991; Nencioni *et al.*, 1991; Leather *et al.*, 1993; Scialli *et al.*, 1993). The former, representative largely of alterations in trabecular bone economy, was variably assessed by double photon absorptiometry, quantitative computed tomography, and even dual energy X-ray absorptiometry (DEXA) technology. Unexpectedly, a wide range of quantitative alterations was noted. Specifically, little or no change in lumbar bone density proved the case in some studies (Tummon *et al.*, 1988; Golan *et al.*, 1989; Damewood *et al.*, 1989). In contrast, losses of up to 8.2% were noted in similarly-studied patient populations (Dodin *et al.*, 1991). Moreover, 5.7 and 4.9% decreases were noted using precise DEXA technology (Surrey and Judd, 1992; Leather *et al.*, 1993). As such, these observations are compatible with the view that the impact of a 6-month course of a GnRHa on lumbar bone density is highly variable. In principle, it is difficult to conceive of an 8.2% bone loss at the level of the lumbar spine occurring within a total of 6 months, given that the worst case scenario in context of the climacteric generally does not exceed 3%/year (Avioli, 1987). A similarly heterogeneous body of information is available for measurements, carried out at the level of the distal radius. Although the reason(s) underlying the high degree of variability and apparent severity of some of the preceding observations remains unknown, serious consideration must be given to the possibility that some of the differences in question may be attributable to the methods of measurement, their level of reproducibility, the involvement of distinct patient

Table III. Effect of GnRHa on bone density

Analogue	Author	Lumbar	Radial
Buserelin	Matta *et al.* (1988a)	−4.6% (QCT)	–
Buserelin	Devogelaer *et al.* (1987)	−2.1% (DPA)	−4.6% (SPA)
Nafarelin	Johansen *et al.* (1988)	−6.0% (DPA)	−4.0% (SPA)
Buserelin	Matta *et al.* (1988b)	−5.9% (QCT)	–
Leuprolide/buserelin	Tummon (1989)	0.0% (DPA)	–
Decapeptyl	Golan *et al.* (1989)	0.0% (DPA)	–
Leuprolide	Damewood *et al.* (1989)	0.0% (DPA)	–
Buserelin	Dawood (1993)	−7.4% (QCT)	0.0% (SPA)
Buserelin	Bianchi *et al.* (1989)	–	0.0% (SPA)
Decapeptyl	Waibel-Treber *et al.* (1989)	↓ (DPA) 15/18 – (DPA) 3/18	0.0% (SPA)
Goserelin	Stevenson *et al.* (1989)	−1.5% (DPA)	–
Decapeptyl	Scharla *et al.* (1990)	↓ (DPA)	0.0% (SPA)
Nafarelin	Whitehouse *et al.* (1990)	−5.9% (QCT)	–
Goserelin	Dodin *et al.* (1991)	−8.2% (DPA)	–
Leuprolide	Rittmaster and Thompson (1990)	−6.3% (DPA)	–
Buserelin	Nencioni *et al.* (1991)	−1.5% (DPA)	−2.1% (SPA)
Leuprolide	Surrey and Judd (1992)	−5.6% (DEXA)	–
Goserelin	Leather *et al.* (1993)	−4.8% (DEXA)	–
Leuprolide	Scialli *et al.* (1993)	−2.9% (DEXA)	–
Leuprolide	Wheeler *et al.* (1993)	−4.3% (DPA; n = 102) −15% (QCT; n = 8)	−0.2% (SPA)
Goserelin	Rock *et al.* (1993)	−5.4% (DPA)	–

QCT = quantitative computed tomography; DPA = double photon absorptiometry; DEXA = dual energy X-ray absorptiometry; SPA = single photon absorptiometry.

Attachment 1.5.

Table IV. Effect of GnRHa therapy on bone turnover parameters

Author	Analogue	Bone formation		Bone resorption		
		Osteocalcin	AP	PO_4	HPR/Cr	Ca/Cr
Gudmundsson *et al.* (1987)	Nafarelin	↑	–	↑	–	↑
Steingold *et al.* (1987a)	Histrelin	–	–	–	↑	↑
Johansen *et al.* (1988)	Nafarelin	↑	↑	↑	↑	↑
Van Leusden and Dogterom (1988)	Decepeptyl	↑	↑	↑	–	–
Waibel-Treber *et al.* (1989)	Decapeptyl	↑	↑	–	–	–
Scharla *et al.* (1990)	Decapeptyl	↑	↑	↑	↑	–
Ylikorkala *et al.* (1990)	Nafarelin	↑	↑	–	–	↑
Riis *et al.* (1990)	Nafarelin	↑	↑	–	↑	–
Dodin *et al.* (1991)	Goserelin	–	↑	–	–	↑
Wheeler *et al.* (1992)	Leuprolide	–	–*	–*	–	–

AP = alkaline phosphatase; HPR = hydroxyproline; Cr = creatinine; Ca = calcium.
*Up to 10% of patients did display treatment-induced changes.

populations, and the employment of highly distinct therapeutic regimens.

Wherever available, limited albeit relatively uniform published information (Table IV) is in keeping with the possibility that the actions of GnRHa at the level of bone involve an overall increase in bone turnover parameters (Steingold *et al.*, 1987; Riis *et al.*, 1990; Gudmundsson *et al.*, 1987; Johansen *et al.*, 1988; van Leusden and Dogterom, 1988; Scharla *et al.*, 1990; Ylikorkala *et al.*, 1990; Dodin *et al.*, 1991). Specifically, note was made of GnRHa-induced increments in parameters reflecting both bone formation (serum osteocalcin and alkaline phosphatase) and bone resorption (serum phosphorous and the creatinine-normalized urinary excretion of hydroxyproline and calcium). Although the precise mechanism(s) whereby GnRHa therapy may promote bone turnover remain uncertain, there is little doubt that the new steady state is due, if only in part, to the hypo-oestrogenic state so induced. Given that the net effect of GnRHa therapy is a decrease in overall bone mineral density, it is highly likely that the GnRHa-induced increase in bone turnover is unbalanced in nature. Specifically, it is highly likely that enhancement of bone resorption exceeds the apparent attendant increase in bone formation.

Yet another critical facet relevant to the impact of GnRHa on bone economy concerns the reversibility of GnRHa-induced bone loss. Indeed, the very premise for the 6-month treatment limit is the presumption that whatever bone loss may accrue in the course of the therapy would prove reversible upon discontinuation of the same. Although the literature offers relatively limited insight into this key issue (Table V), several (Devogelaer *et al.*, 1987; Johansen *et al.*, Matta *et al.*, 1988a), but by no means all reports are in keeping with the observation that discontinuation of treatment will be associated with a virtually complete recovery of bone loss when evaluated 6 months following discontinuation of therapy. Indeed, a small but persistent body of literature appears to suggest that the GnRHa-induced bone loss may not be entirely reversible and may in fact be characterized by a net decrease in bone density of up to 5.4% when assessed 6 months after discontinuation of therapy (Dodin *et al.*, 1991). A recent report employing precise DEXA technology suggested incomplete recovery at 6 months, the residual bone loss being 4.2% (Riis *et al.*, 1990).

Table V. Recovery of bone density following GnRHa therapy

Author	Analogue	Follow-up (months)	Recovery
Devogelaer *et al.* (1987)	Buserelin	3	Virtually complete
Johansen *et al.* (1988)	Nafarelin	6	Complete
Matta *et al.* (1988a)	Buserelin	6	Complete
Dawood (1989)	Buserelin	6	Incomplete (−4.2%)
Waibel-Treber *et al.* (1989)	Decapeptyl	6–9	7/9 complete 2/9 incomplete
Stevenson *et al.* (1989)	Goserelin	6	None (−1.5%)*
Whitehouse *et al.* (1990)	Nafarelin	6	Incomplete (−2.0%)*
Rittmaster (1988)	Leuprolide	12	Incomplete (−1.9%)
Dodin *et al.* (1991)	Goserelin	6	Incomplete (−5.4%)*
Nencioni *et al.* (1991)	Buserelin	6	None (−3%)
Surrey (1992)	Leuprolide	6	Incomplete (−4.2%)
Wheeler (1993)	Leuprolide	12	Incomplete (up to −2.6%)
Rock *et al.* (1993)	Goserelin	12–18	Incomplete (up to −7.6%)

*Not statistically significant or not evaluated for statistical power.

All told, the current literature suggests that treatment with GnRHa for 6 months may be associated with a significant and not necessarily reversible decrease in bone mineral density, an effect due to enhanced (presumably unbalanced) bone turnover. Besides highlighting the need for additional studies, these observations strongly suggest that steroid 'add-back' is likely to prove indispensable to bone health in the context of long-term (and quite possibly short-term) GnRHa application.

Objectives, advantages and disadvantages of steroid 'add-back' therapy

As might be anticipated from the complex of symptoms characterizing the GnRHa-induced hypo-oestrogenic state, the objectives of steroid 'add-back' therapy would be to provide

cardioprotection as well as prevent bone loss, hot flushes, and urogenital atrophy. In this respect, 'steroid add-back' therapy is not unlike standard hormone replacement therapy as applied in the context of the menopausal state.

Although the potential advantages of 'add-back' therapy would appear self-evident, the following listing of benefits appears worthy of further emphasis: (i) diminution of some or all of the side effects associated with GnRHa therapy; (ii) provision of a medical treatment option to patients representing a high surgical risk. Accordingly, patients in whom surgical intervention is contra-indicated for medical reasons may benefit from long-term therapy, an option previously receiving relatively limited attention; (iii) delaying (virtually indefinitely) surgical intervention if desired. Indeed, 'add-back' therapy has the potential of providing flexibility not possible with a limited (6 months) course of therapy as regards the surgical scheduling of anticipated or inevitable surgical procedure. The above notwithstanding, steroid 'add-back' therapy is not without its relative shortcomings. Firstly, long-term steroid 'add-back' treatment may delay tissue diagnosis in that the surgical intervention is either bypassed or postponed. Indeed it is not inconceivable that under such circumstances, the diagnosis of prognostically poor entities such as uterine sarcoma may be missed or overlooked. Although the incidence of such occurrence is likely to be relatively limited, precedents already exist (Hitti *et al.*, 1991). The reason why such a condition is likely to be rare has to do with the fact that the overall incidence of uterine sarcoma is 1.7/100 000 women age 20 years or more. Secondly, it goes without saying that provision of steroid 'add-back' therapy at this time will be associated with increased cost reflecting largely the GnRHa component. Furthermore, given that steroid 'add-back' therapy is not Food and Drug Administration (FDA)-approved at this time as a therapeutic strategy, no reimbursement can at this time be anticipated from third party payers. Lastly, given the absence of an orally administered GnRHa, current long-term GnRHa/steroid 'add-back' therapy would require a parenteral route of GnRHa administration (i.m., s.c., or intranasally).

Clinical indications for GnRHa/steroid 'add-back' regimens

Given the relatively short history of the very concept of GnRHa/steroid 'add-back' therapy, the indications for such an approach are still in a stage of evolution (Table VI). Although preliminary, the following list constitutes an example of promising clinical entities to be targeted:

Symptomatic endometriosis in individuals not desirous of pregnancy

In this case, the individuals most likely to benefit from a GnRHa/steroid 'add-back' regimen are those in whom GnRHa therapy for symptomatic endometriosis has to be prematurely discontinued following a 6-month course. Given that the 'grace' period to follow is likely to be limited, the individuals in question invariably request continued relief. Unfortunately, repeated courses of GnRHa therapy, although feasible, have not been approved as such and do not at this time constitute the standard of care for fear of substantial, cumulative bone loss. Consequently, if one were to wish to provide continued sustained relief, long-term GnRHa administration with steroid 'add-back' protection would prove highly desirable. It is equally likely that incidentally discovered endometriosis (e.g. in the course of an appendectomy) could benefit from long-term prophylaxis by way of a GnRHa/steroid 'add-back' regimen. Clearly, no such option exists at this time thereby dooming the patients in question to progressive aggravation of the endometriotic state to a point where it may become symptomatic and/or causally related to future infertility.

Table VI. Potential indications for 'add-back' therapy

(1)	Symptomatic endometriosis (pregnancy not recommended)
(2)	Symptomatic uterine fibroids
(3)	Ovarian hyperandrogenism
(4)	Premenstrual syndrome
(5)	? Menopausal transition
(6)	? Dysfunctional uterine bleeding
(7)	? Breast cancer prevention

Symptomatic uterine fibroids in individuals who are either ineligible or do not wish definitive surgical therapy

Falling under this heading are a large number of patients in their early 40s who could in principle be carried on a medical regimen into the menopause at which point the very issue of the uterine fibroid may become non-applicable.

Ovarian hyperandrogenism

Reserved primarily for individuals with moderate to severe ovarian hyperandrogenism, long-term GnRHa/steroid 'add-back' therapy has been practised for some time (Chang *et al.*, 1983; Faure and Lemay, 1986; Andreyko *et al.*, 1986; Mongioi *et al.*, 1986; Cousinet *et al.*, 1986; Steingold *et al.*, 1987; Calogero *et al.*, 1987; Schaison and Couzinet, 1987; Rittmaster, 1988; Faure and Lemay, 1988; Adashi, 1990; Falsetti *et al.*, 1992). Clearly, this clinical circumstance is unique in that there is no contra-indication *a priori* for the use of steroid 'add-back' therapy. Indeed, the very purpose of the therapy is only to lower the circulating concentrations of androgens. In this case, the replacement of sex steroids does not in any way undermine the purpose of the therapy and as such is perfectly compatible with the therapeutic objectives. Considering that GnRHa constitutes the most potent means available to date for the suppression of the reproductive axis, the long-term use of these principles could clearly benefit individuals severely affected by this chronic condition.

Premenstrual syndrome

Although the precise aetiology of the premenstrual syndrome remains a matter of study, efforts directed at interrupting the

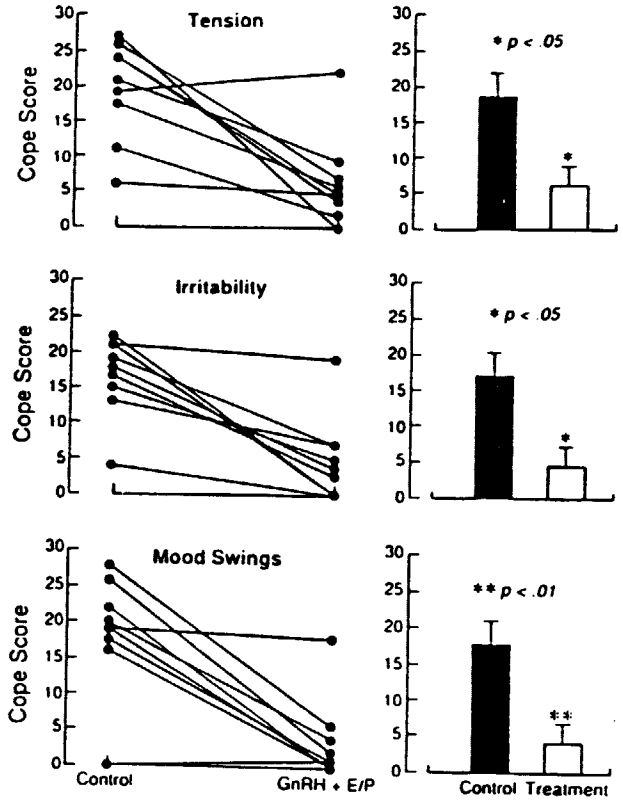

Fig. 1. Left panels, total calendar of pre-menstrual experiences (COPE) scores for tension, irritability, and mood swings for individual subjects during the luteal phase during months in which subjects were administered gonadotrophin-releasing hormone agonist (GnRHa) daily in addition to conjugated equine oestrogen (CEE) on days 1–25 and medroxyprogesterone acetate (MPA) on days 5–25 (GnRH = oestrogen/progestin). Right panels, mean scores for the eight women during the control and GnRHa and oestrogen/progestin month (treatment). Reproduced with permission from Mortola *et al.* (1991).

cyclic nature of this clinical entity have proved of some value. This issue has been most directly addressed by Mortola *et al.* (1991) (Figure 1), whose study clearly revealed that the long-term application of a GnRHa together with steroid 'add-back' therapy could prove useful in the context of the premenstrual syndrome (Mortola, 1991). Here again, the clinical condition is uniquely suited for steroid 'add-back' therapy in light of the fact that sex steroid replacement may be perfectly compatible with the objectives of therapy.

In a double-blind placebo-controlled study (Leather *et al.*, 1993), 60 women aged 21–45 years were randomized to one of three treatment groups: placebo implant every 4 weeks plus placebo oestrogen replacement therapy tablets daily, goserelin (3.6 mg) implants every 4 weeks plus placebo oestrogen replacement therapy tablets daily, or goserelin (3.6 mg) implants every 4 weeks plus oestradiol valerate (2 mg/day) with norethindrone (5 mg from days 22–28). DEXA scans were performed before treatment and again after six treatment cycles. Note was made of the fact that the oestrogen/progestin 'add-back' therapy prevented any change in bone density as compared with either pre-treatment values or the group receiving placebo plus placebo. The study must be qualified by the recognition of a drop-out rate of 32%. All told, this study suggests, if nothing else, the ability of the oestrogen/progestin regimen to protect women from bone loss at the level of the lumbar spine and femoral neck for the 6 months of the therapy.

Menopausal transition

Although relatively limited attention has been paid to the menopausal transition as a distinct clinical entity, such recognition appears long overdue. This component of the reproductive life cycle is commonly and unfortunately afflicted by a series of complications for which no specific uniformly effective therapy is currently available. 'Easing' women into the menopause by way of combination oral contraceptive- or GnRHa-induced suppression of reproductive function until the actual menopause sets in could prove to be a useful strategy. For the latter, no obvious contra-indication would exist for the replacement of sex steroids in that the artificial induction of a reversible menopause-like state virtually requires some form of sex steroid replacement.

Dysfunctional uterine bleeding

This often debilitating clinical circumstance has proven difficult to manage. In an effort to provide an improved therapeutic option, several investigators examined the possibility of utilizing a long-term therapeutic approach with GnRHa combined with steroid 'add-back' therapy. In one such case, use was made of s.c. administered leuprolide at a dose of 1 mg/day (Fedorkow *et al.*, 1989). This in turn was supplemented with transdermal oestrogen therapy 50 μg/day twice weekly followed by the sequential administration of medroxyprogesterone acetate (MPA) at a dose of 10 mg/day between days 21–28 of each cycle. This approach resulted in regular withdrawal bleeding of normal volume and stabilized the haematological parameters for the duration of the therapy.

Similarly, Thomas *et al.* (1991) carried out an open observational study comparing menstrual blood loss before, during and after 3 months of treatment with a combination of a long-acting GnRHa and cyclic hormone replacement therapy. A total of 20 women complaining of heavy menstrual loss participated in the study. The drugs employed included depot goserelin along with cyclic hormone replacement therapy (1 mg of cyclo-progynova). Although quantitative assessment was subject to obvious limitations, the evidence suggested a decrease in overall menstrual loss.

More recently, Vercellini *et al.* (1993) reported on the case histories of 23 subjects whose chronic anovulatory bleeding pattern (associated with severe iron-deficiency) was managed for 6 months with depot goserelin. Monitored before and after this course of therapy, the patients in question displayed an increase in the circulating concentrations of haemoglobin from 0.79–1.38 g/ml, comparable increments being noted for the haematocrit (from 26–41.6%), the serum iron (from 1.98–6.33 μg/ml), and serum ferritin (from 6.2–35.3 ng/ml). The endometrial hyperplasia observed in 11 subjects displayed regression at the time of a follow-up suction biopsy. These observations support

Table VII. Studies on effect of 'add-back' progestins

			Endometriosis			
Author	Year	No. of subjects	Analogue	Dose*	Progestin	Dose**
Riis *et al.*	1990	17	Nafarelin	400	NE	1.2
Surrey *et al.*	1990	10	Histrelin	100	NE	0.35–3.5
Cedars *et al.*	1990	8	Histrelin	100	MPA	20–30
Surrey and Judd	1992	10	Lupron	3.75***	NE	5–10

*μg/day.
**mg/day.
***mg/month.
NE = norethindrone; MPA = medroxyprogesterone acetate.

the utility of GnRHa in the context of acute severe dysfunctional uterine bleeding associated with iron-deficiency anaemia. Clearly, this form of therapy cannot be expected to rectify the underlying anovulatory disorder; however, a short-term treatment course might indeed allow for haematological recovery and hence a more leisurely discussion of long-term disposition.

Breast cancer prevention

To initially address the possibility of preventing breast cancer with a long-term regimen of GnRHa along with steroid 'add-back' therapy, Spicer *et al.* (1993) and Judson (1993) have examined a prototype contraceptive consisting of a depot Lupron preparation administered i.m. (7.5 mg) every 28 days complemented with low doses of an oral oestrogen (0.625 mg of conjugated oestrogen for 6 days every week) and intermittent oral progestogen (10 mg of MPA for 13 days every 4 months). In all, 18 subjects previously shown to display a five-fold or greater increased breast cancer risk were involved and randomized as follows: 12 of the patients were assigned to the contraceptive arm whereas six of the patients were assigned to the control arm. For the most part, scheduled vaginal bleeding was observed. More importantly, a beneficial rise was noted in the circulating concentrations of HDL cholesterol in the treatment group. However, despite the employment of an oestrogen dose known to protect post-menopausal women from bone loss, a total annual loss of 1.9% was detected in the treatment group. Conceivably, the latter decrease may have represented inhibition of ovarian androgen production by the GnRHa. This preliminary study is anticipated to prove a forerunner for additional studies in this area before too long.

Endometriosis: progestin only 'add-back' regimens

Studies concerned with the long-term application of GnRHa in the context of endometriosis have thus far only employed progestins as the 'add-back' steroid of choice (Table VII). Specifically, use has been made of the 17α-hydroxyprogesterone derivative MPA (provera) and of the 19-nortestosterone derivative norethisterone (also known as norethindrone; NET). Clearly, the choice of progestin-only regimens was dictated in part by the

Table VIII. Impact of 'add-back' progestins

		Endometriosis	
Author	Regimen	Bone mineral density	
		Lumbar	Radial
Riis *et al.* (1990)	Nafarelin/ norethindrone	– (DPA)	– (SPA)
Surrey *et al.* (1990)	Histrelin/ norethindrone	↓ (QCT)	– (SPA)
Cedars *et al.* (1990)	Histrelin/ MPA	– (QCT)	– (SPA)
Surrey and Judd (1992)	Lupron/ norethindrone	↓ (DEXA)	– (SPA)

SPA = single photon absorptiometry; DPA = double photon absorptiometry; QCT = quantitative computed tomography; DEXA = dual energy X-ray absorptiometry.

reluctance on the part of several investigators to employ oestrogenic principles, the ability of which to aggravate or activate the underlying endometriotic process constitutes a possibility (Dick *et al.*, 1992; Goodman *et al.*, 1989; Habuchi *et al.*, 1991; Kiely *et al.*, 1988; Plous *et al.*, 1985; Ray *et al.*, 1985; Kapadia *et al.*, 1984). Moreover, progestins appear uniquely suited as an 'add-back' agent by virtue of their established ability to promote endometrial atrophy. Clearly, this direct effect on endometrial implants, sometimes referred to as a 'pseudopregnancy' effect, has been at the centre of therapeutic strategies for endometriosis for some time (Moghissi and Boyce, 1976; Telimaa *et al.*, 1987; Hull *et al.*, 1987; Luciano *et al.*, 1988; Haney and Weinberg, 1988; Roland *et al.*, 1976). In this sense, the addition of a progestin only to a long-term GnRHa regimen provides for a multi-pronged attack on the pathophysiology of the disease. Above and beyond these considerations, synthetic progestins have been demonstrated to be capable of ameliorating vasomotor symptoms and of retarding both urinary calcium excretion and radiologically studied bone loss (Appleby, 1962; Bullock *et al.*, 1975; Gallagher and Nordin, 1975; Schiff *et al.*, 1980; Nordin *et al.*, 1980; Albrecht *et al.*, 1981; Dequeker and Demuylder, 1982; Paterson, 1982; Mandel *et al.*, 1982; Lobo *et al.*, 1984; Selby *et al.*, 1985; Abdalla *et al.*, 1985; Horowitz *et al.*, 1987; Prior, 1990; Cundy *et al.*, 1991;

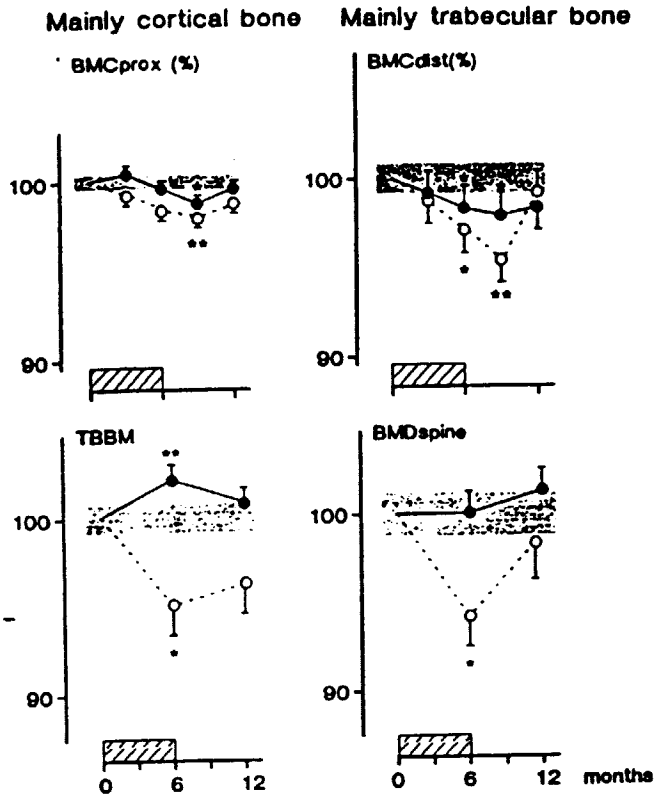

Fig. 2. Mean (±SEM) changes in bone mineral (percentage) during treatment and after withdrawal in the groups treated with -lin plus notethindrone (NET; solid circles) and nafarelin alone circles). The grey bars indicate the variation in changes l year in the control group (mean ± average SEM). *, $P < 0.05$; **, $P < 0.01$ (versus. baseline). BMC = bone mineral content; Prox/Dist = proximal and distal thirds of the forearm; TBBM = total body bone mineral; BMD spine = bone mineral density in the lumbar spine (L2–L4). Reproduced with permission from Riis *et al.* (1990).

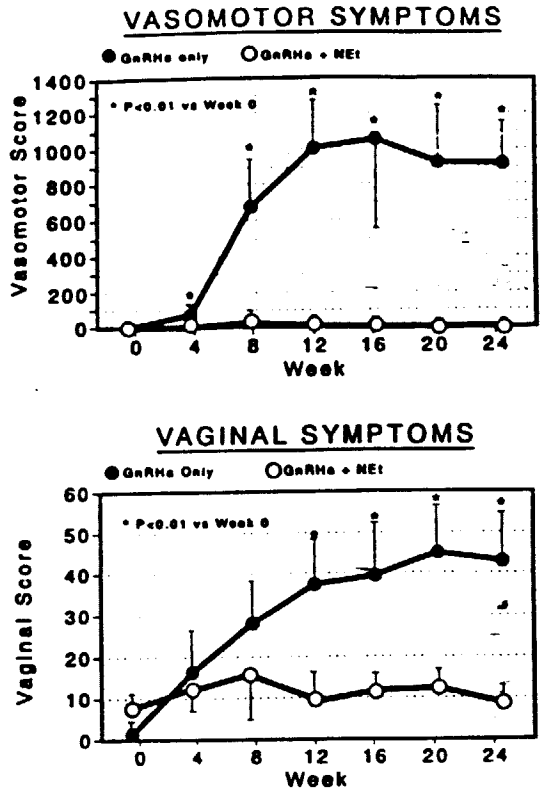

Fig. 3. Impact of a progestin (norethindrone)-only 'add-back' regimen on vasomotor symptoms and vaginal symptoms. Reproduced with permission from Surrey and Judd (1992).

Gallagher *et al.*, 1991), thereby addressing some of the side-effects associated with the GnRHa-induced hypo-oestrogenic state.

Using the above-mentioned strategy, a total of four studies have thus far been reported (Surrey and Judd, 1992; Riis *et al.*, 1990; Cedars *et al.*, 1990; Surrey *et al.*, 1990), the subjects under study totalling 55. Clearly then, the information provided must be viewed as preliminary. The individuals in question were treated by different agonists (nafarelin, leuprolide, or histrelin) as well as different synthetic progestins (NET or MPA). Moreover, the doses employed proved highly variable.

Evaluated in terms of impact on bone mineral density (Table VIII), progestin-only 'add-back' was uniformly judged to virtually eliminate the GnRHa-induced decrease in radial bone density as assessed by single-photon absorptiometry (Riis *et al.*, 1990; Cedars *et al.*, 1990; Surrey *et al.*, 1990). Similarly, combinations afarelin/NET (Figure 2) or histrelin/MPA proved fully ctive for the lumbar spine assessed by means of double-photon absorptiometry (Riis *et al.*, 1990) and quantitative computed tomography (Cedars *et al.*, 1990; Surrey *et al.*, 1990). In contrast, treatment with histrelin (100 μg/day)/NET (0.35–3.5 mg/day) failed to protect the individuals in question from a GnRHa-induced decrease in lumbar bone density as assessed by quantitative computed tomography (Cedars *et al.*, 1990). Similarly, that the use of depot leuprolide in conjunction with 5–10 mg of norethindrone was still associated with a decrease of 2.7% in lumbar bone density was established 6 months into the therapy. This observation appears particularly relevant in that bone density was assessed by precise contemporary technology, i.e. DEXA (Surrey and Judd, 1992). Although a larger number of patients would be required to confirm the preceding observations, the preliminary data available would suggest that appropriately-tailored progestin 'add-back' therapy may well prove protective with respect to the otherwise inevitable GnRHa-induced decrease in bone mineral density.

Evaluated in terms of their ability to combat GnRHa-induced hot flushes, both NET (Figure 3) and MPA (not shown) decreased the overall hot flush score experienced by the women under study (Surrey and Judd, 1992; Cedars *et al.*, 1990; Surrey, *et al.*, 1990). Although no firm quantitative conclusions can be drawn, NET (Surrey and Judd, 1992; Surrey *et al.*, 1990), at the doses used, appeared more active then MPA (Gallagher *et al.*, 1991).

Evaluated in terms of their impact on the disease process as assessed by pain scores and a second look laparoscopy, NET and MPA yielded fundamentally different results. Indeed, given combinations of histrelin/NET or leuprolide/NET (Figure 4), a meaningful decrease in the extent of endometriosis was noted

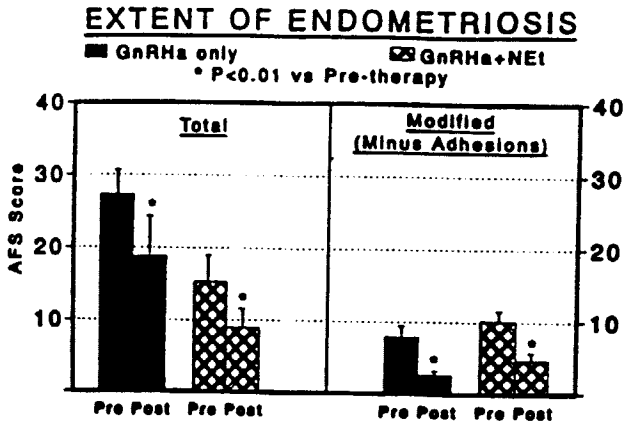

Fig. 4. Impact of a progestin (norethindrone)-only 'add-back' regimen on the extent of endometriosis as assessed by the American Fertility Society score. Reproduced with permission from Surrey and Judd (1992).

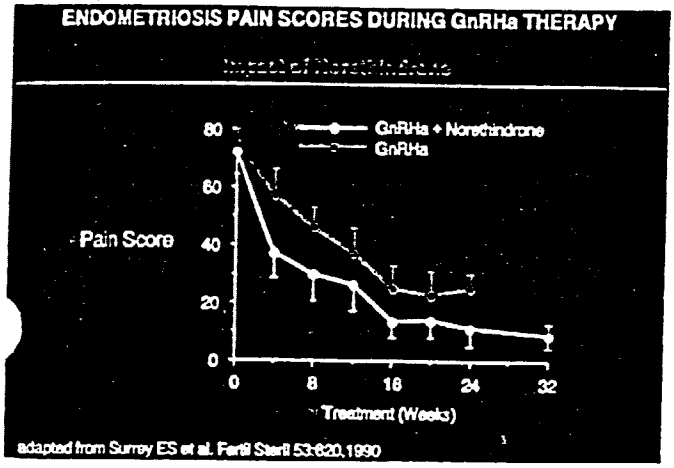

Fig. 5. Impact of a progestin (norethindrone)-only 'add-back' regimen on the pain score associated with symptomatic endometriosis. Adapted from Surrey *et al.* (1990).

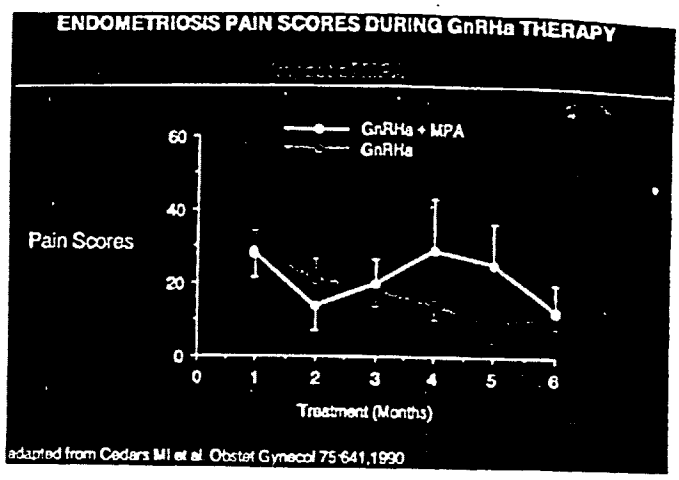

Fig. 6. Impact of progestin (MPA)-only 'add-back' regimen on the pain score associated with symptomatic endometriosis. Adapted from Cedars *et al.* (1990).

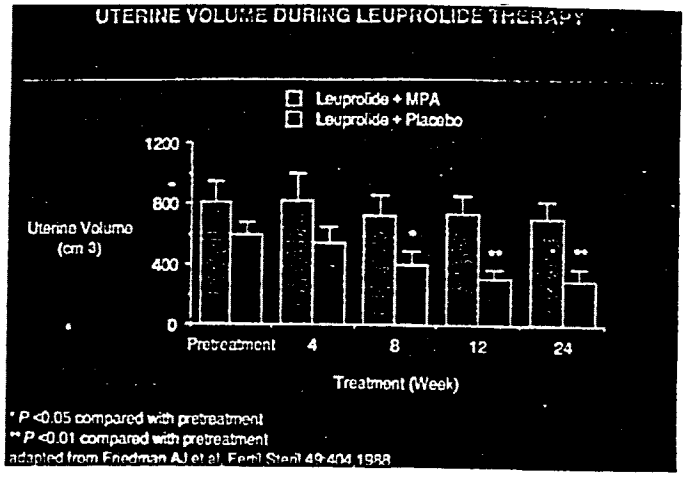

Fig. 7. Effect of concurrent progestin (MPA)-only 'add-back' on the ability of leuprolide to reduce the sonographically monitored uterine volume. Adapted from Friedman *et al.* (1988).

(Surrey and Judd, 1992; Surrey *et al.*, 1990). In contrast, MPA virtually antagonized the salutary effect of histerelin when assessed for the very same end points by Cedars *et al.* (1990). Evaluated over a 32-week period, NET (Figure 5) clearly produced a meaningful decrease in the pain score experienced by the patients under study (Surrey *et al.*, 1990). In contrast, pain scores reported by patients given a combination of histrelin and MPA (Figure 6) did not differ from those reported by patients on histrelin alone (Cedars *et al.*, 1990). As such, these findings suggest that MPA, unlike NET, may in fact antagonize the therapeutic efficacy of GnRHa in the context of endometriosis. In the light of these findings, serious consideration must be given to the question of whether the apparent ability of MPA to undermine the efficacy of GnRHa therapy is limited to endometriosis. The answer to this question requires the assessment of similar agonist/MPA combination in other clinical contexts. One such example is the work of Friedman *et al.* (1988) wherein GnRHa/MPA regimens were employed to reduce the uterine volume in patients afflicted with uterine fibroids. As expected, patients provided with the GnRHa by itself displayed the predictable 50% decrease in uterine volume 3 months into the therapy. However, the concurrent provision of MPA all but eliminated the salutary effect of GnRHa (Figure 7). As such, these findings indicate that MPA inexplicably may antagonize the beneficial effects of GnRHa in the context of both endometriosis and uterine fibroids. Although the mechanism(s) responsible for this enigmatic action remain uncertain, it would appear prudent at this time to avoid this progestin supplement until such time that the issue is clarified by larger scale clinical studies.

Complementing the preceding observations, is a pilot study concerned with the application of low dose buserelin (daily) and MPA (monthly). Specifically, use was made of 400–600 μg of buserelin, once daily, together with periodic MPA to treat selected patients with chronic endometriosis, dysmenorrhoea and menorrhagia (Lemay and Dewailly, 1989). It was the objective

of the study to evaluate the effects of a dose regimen that would maintain oestradiol concentrations low enough to relieve symptoms but high enough to avoid side effects, while allowing uterine bleeding following monthly progestagen administration. Reportedly, side-effects were few and minor and may have reflected the attendant hypo-oestrogenism. Two patients reported occasional hot flushes and one patient had several hot flushes daily. Vaginal lubrication decreased in two patients but did not cause dyspareunia. The circulating concentrations of LDL and HDL were largely unchanged. Bone mineral density evaluated by double-photon-absorptiometry at the level of the lumbar spine displayed a decremental tendency after 6 months of treatment. Calcium excretion was increased in two of the patients.

As stated earlier, the literature thus far appears limited to the use of GnRHa/progestin combinations in the context of endometriosis. However, a recent case report would appear to suggest that the combination of a GnRHa and a combined continuous oestrogen/progestin regimen may be of value (Reid *et al.*, 1992). The case in question, suffering from severe endometriosis, failed to respond to high dose MPA (50 mg/day) and to Danazol (200 mg/ t.i.d.). Given that the surgical option has been ruled out by the patient, consideration was given to the monthly use of s.c. goserelin (3.6 mg/month) supplemented by 0.625–5.0 mg of conjugated oestrogens and 5 mg of MPA daily. Aside from providing symptomatic relief, this treatment combination was associated with amenorrhoea, painless intercourse, normal bowel function, and normal body weight. . 'depression' previously reported and ascribed to the use of progestins has all but dissipated. Pelvic examination revealed softening of a rectal/vaginal mass and diminution in rectal constriction. Bone density studies carried out 12 months after the onset of treatment confirmed maintenance of stable bone density. As such, this limited information raises the prospect of complex regimens which may allow the safe long-term application of GnRHa in individuals with endometriosis.

Along similar lines, Friedman and Hornstein (1993) have recently set out to assess the safety and efficacy of leuprolide acetate depot plus daily conjugated oestrogens and MPA 'add-back' therapy in the context of endometriosis-associated pelvic pain. This limited retrospective pilot study involved eight patients, all of whom reported moderate to severe pelvic pain in association with laparoscopically documented endometriosis. Leuprolide acetate depot was provided i.m. at a dose of 3.75 mg every 4 weeks for 24 months. Oral conjugated equine oestrogens were provided at the dose of 0.625 mg/day along with medroxyprogesterone acetate 2.5 mg/day from treatment months 3–24. Clear-cut beneficial effects were noted in the extent of endometriosis as well as in reported pelvic pain scores. Interestingly, DEXA bone density measurements of the lumbar spine remained essentially unchanged during the two year study period. As expected, a substantially reduced incidence of hot flushes was noted. In summary, the authors interpreted the results to suggest that in this small retrospective study, the regimen under evaluation proved effective for the therapy of women with endometriosis-associated pelvic pain.

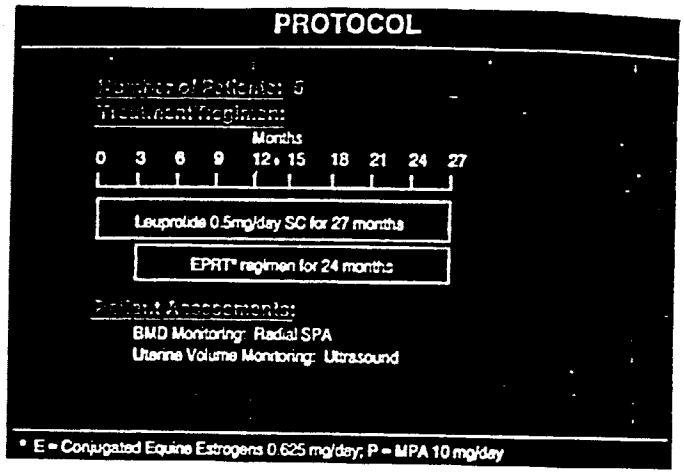

Fig. 8. Protocol of a non-concurrent oestrogen/progestin 'add-back' regimen designed to treat uterine fibroids. Adapted from Friedman (1989).

Uterine fibroids: oestrogen/progestin 'add-back' regimens

Unlike patients with endometriosis, who were subjected to progestin-only 'add-back' regimens, patients with uterine fibroids have been the subject of several preliminary studies wherein oestrogen/progestin 'add-back' regimens were employed.

First among these is a preliminary study by Friedman (1989a), the objectives of which were to examine the impact of an oestrogen/progestin 'add-back' regimen on the growth of uterine fibroids and on bone economy. Limited in scope, involving only five patients, the study (Figure 8) entailed the s.c. administration of the GnRHa lupron for a total of 27 months at a daily dose 0.5 mg. At the 3-month time point, oestrogen/ progestin replacement therapy was superimposed on the GnRHa regimen and maintained for the remainder of the 24-month study. The oestrogen/progestin regimen in question consisted of the sequential application of conjugated equine oestrogens at a daily dose of 0.625 mg followed by the administration of MPA (10 mg/day between days 16–25 of each calendar month). Given this approach, the patients under study received the full benefit of GnRHa therapy for a total of 3 months, a time interval during which most of the therapeutic effect had been achieved. Consequently then, it was the ability of the superimposed oestrogen/progestin regimen to reverse the salutary effect of the GnRHa which was evaluated. Therapeutic end-points included the monitoring of uterine volume by ultrasound and the monitoring of bone mineral density by single-photon absorptiometry measurements at the level of the distal radial bone.

As shown (Figure 9), treatment with the GnRHa for 3 months produced the expected decrements in uterine volume as assessed sonographically. The overall decrease approximated 50%, in

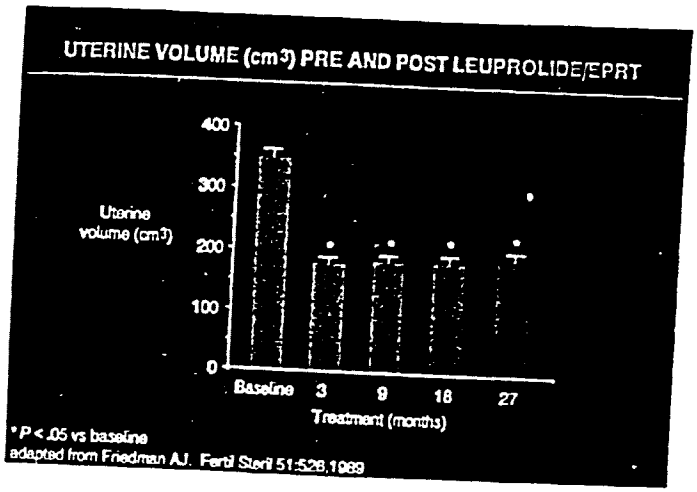

Fig. 9. Impact of a non-concurrent oestrogen/progestin 'add-back' regimen on sonographically monitored uterine volume. Adapted from Friedman (1989).

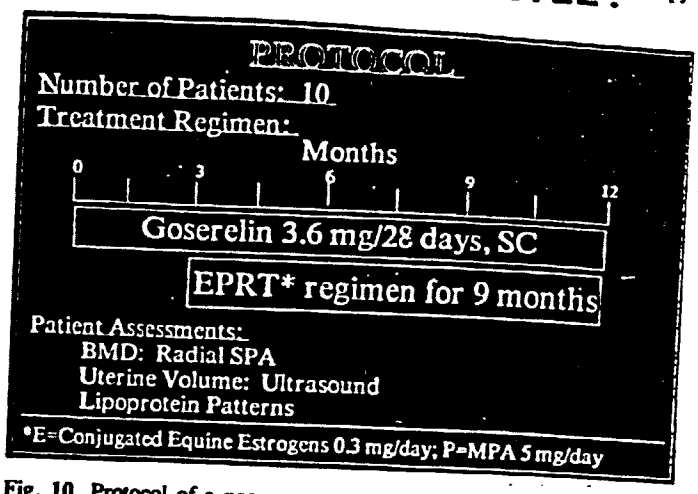

Fig. 10. Protocol of a non-concurrent oestrogen/progestin 'add-back' regimen designed to treat uterine fibroids. Adapted from Maheux *et al.* (1991).

Table IX. Bone density of the radius: effect of leuprolide/oestrogen/progestin replacement therapy (EPRT)

	Bone density (g/cm³)	
	Distal radius	Ultradistal radius
Baseline	0.76 ± 0.05	0.37 ± 0.05
3 months	0.74 ± 0.05	0.36 ± 0.06
9 months	0.75 ± 0.05	0.37 ± 0.05
18 months	0.76 ± 0.04	0.36 ± 0.05
27 months	0.75 ± 0.03	0.36 ± 0.04

Adapted from Friedman (1989).

keeping with earlier observations. More importantly, however, superimposition of an oestrogen/progestin replacement regimen at this time, failed to reverse the therapeutic effect of the GnRHa. Moreover, the oestrogen/progestin regimen provided appeared to protect the patients in question from loss of bone density as assessed at the level of the distal and ultradistal radius for the duration of the study (Table IX).

A similar study was recently reported by Maheux *et al.* (1991) wherein a total of 10 patients had been evaluated. Specifically, use was made of goserelin (3.6 mg/ 28 days s.c.) administered for a total of 12 months (Figure 10). Following 3 months of treatment with the GnRHa by itself, an oestrogen/progestin replacement regimen was superimposed for the remaining 9 months. The latter consisted of conjugated equine oestrogens 0.3 mg/day and the sequentially applied MPA at a dose of 5 mg/day. The patients in question were monitored for their bone mineral density at the lumbar and femoral level, uterine volume measurements being carried out by ultrasound. In addition, the circulating lipoprotein pattern was monitored as well.

As expected, treatment with goserelin for 3 months resulted in the projected 50% decrease in uterine volume as monitored by sonography (Figure 11). Importantly, however, superimposition of the oestrogen/progestin replacement regimen

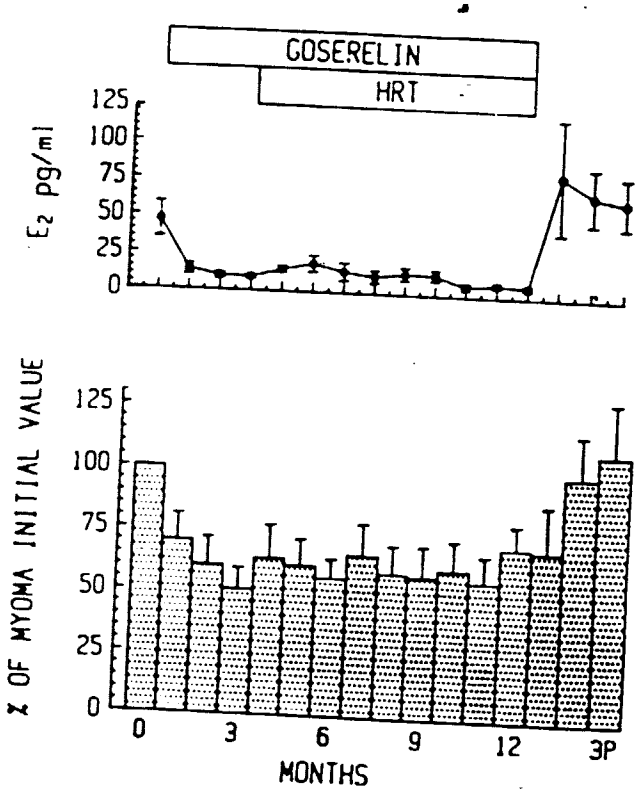

Fig. 11. Impact of an oestrogen/progestin 'add-back' regimen on circulating oestradiol (E_2) concentrations or on sonographically monitored volume (% of myoma initial value). Reproduced with permission from Maheux *et al.* (1991).

failed to antagonize the salutary effect of the GnRHa. However, discontinuation of therapy resulted in prompt reversal of the therapeutic gains in keeping with the recognition that the therapy is entirely reversible. Importantly, no significant decrements were noted in bone mineral density (Table X) at the lumbar and femoral levels. Similarly, no significant adverse effect was noted on the circulating lipoprotein pattern (Table XI). Taken together, these findings suggest that the oestrogen/progestin 'add-back'

Attachment 1.13.

Table X. Impact of oestrogen/progestin 'add-back' on bone mineral density

Site	Duration of treatment (months)					
	0	3	6	9	12	+3
Lumbar (g/cm^2)	1.17	1.17	1.02	1.02	1.04	1.14
Femoral	0.89	0.88	0.79	0.76	0.76	0.85
n	10	10	9	9	8	10

Table XI. Impact of oestrogen/progestin 'add-back' on lipid parameters

Parameters (mmol/l)	Duration of treatment (months)					
	0	3	6	9	12	+3
Cholesterol	4.8	5.3	5.2	5.1	5.0	5.0
HDL-cholesterol	1.8	1.9	1.8	1.8	1.8	1.8
Triglycerides	0.9	1.0	1.2*	1.2	1.2	0.8
LDL-cholesterol	1.8	1.9	2.1*	2.1*	2.1	1.9
n	10	10	9	9	8	10

*$P < 0.05$.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

replacement regimen does not adversely effect uterine volume or peripheral bone density during GnRHa therapy. An expanded report followed (Maheux and Lemay, 1992).

More recently, West *et al.* (1992) reported on the use of the GnRHa/MPA combination in the management of 20 women with symptomatic uterine fibroids. This open pilot study compared two protocols. In one, 10 women received goserelin 3.6 mg monthly combined with MPA (15 mg/day) for 6 months. Under those circumstances, the uterine volume measured by ultrasound decreased by only 18% after 3 months, no further decrements being noted at the 6-month time-point. The other 10 received goserelin alone for the initial 3 months, followed by combined treatment for three additional months. In this case, note was made of a 39% decrease in uterine volume at the 3-month time point with no significant regrowth by 6 months. Studied 6 months post-therapy, uterine volume has not returned to pre-treatment size. In either treatment group, MPA significantly reduced the frequency of hot flushes. As such, these findings confirm the ability of MPA to antagonize GnRHa action when provided concurrently. However, these findings further indicate that the application of MPA after initial suppression by GnRHa had no adverse effect on uterine volume thereby suggesting the utility of this principle if applied under the circumstances described.

In a more recent contribution, Friedman *et al.* (1993) reported on a two year study wherein 51 pre-menopausal women with large, symptomatic uterine fibroids were evaluated for the impact of steroid 'add-back' therapy in the context of long-term GnRHa therapy. Specifically, the subjects in question received depot on every 4 weeks for 12 weeks, during which time domization to oestrogen-progestin or progestin-only was established for the subsequent 92 weeks of therapy. Reporting

Table XII. Pros and cons of 'add-back' therapy

Steroid 'add-back' therapy may:
1. Diminish some or all of the side-effects associated with gonadotrophin-releasing hormone agonist therapy.
2. Provide a medical treatment option to patients who present with high surgical risk.
3. Delay surgical intervention more or less indefinitely if desired.
4. Delay tissue diagnosis.
5. Incur significant costs.
6. Entail a parenteral route of administration.

on the first 52 weeks of the study, Friedman *et al.* (1993) observed no significant regrowth of uterine volume in the oestrogen-progestin 'add-back' group. In contrast, the progestin 'add-back' group displayed a mean uterine volume of 92% of pre-treatment size. The progestin 'add-back' group displayed a significant decrease in the circulating concentrations of HDL, an effect absent in the oestrogen-progestin 'add-back' group. Although 3% of bone loss was noted during the first 12 weeks of therapy, the subsequent provision of steroid 'add-back' resulted in complete normalization.

In yet another related study, Carr *et al.* (1993) set out to prospectively compare the utility of MPA (20 mg/day) in either the first or last 12-week period of a 6-month treatment course of GnRHa (lupron; 1 mg/day). Specifically, 16 women were randomized to receive either MPA or placebo, only to be crossed over at 12 weeks to placebo or MPA, respectively, for the final 12 weeks of the treatment interval. The results suggested that MPA may well reverse the effectiveness of GnRHa, thereby confirming earlier statements to this effect.

Future directions

The concept of 'steroid add-back' therapy as a supplement to long-term GnRHa application is a novel and important one. However, current information bearing on the utility of this approach in a variety of clinical entities is still sparse. Accordingly, large scale prospective clinical studies will have to be carried out to establish the utility of this approach. On theoretical grounds alone, it should perhaps be possible to achieve a level of oestrogenic replacement which is compatible with the amelioration of the hypogonadal symptoms, as well as with maintenance of the therapeutic effect of GnRHa. This theoretical level of circulating and tissue oestrogens, referred to as the 'oestrogen threshold' (Barbieri, 1990a,b,1992; Friedman *et al.*, 1990; Barbieri and Gordon, 1991; Hodgen, 1991; Judd, 1992) is at the heart of current therapeutic trials. According to this view, the pros and cons of therapy (Table XII) can be balanced and tissue sensitivity to oestrogen may be variable thereby allowing the protection of bone, heart and urogenital tissues without activating the relatively insensitive endometriotic or fibroid targets. Whether or not the 'oestrogen threshold' hypothesis can in effect be proven correct remains a matter for future studies.

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Received on October 25 1993; accepted on January 22, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S22

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 8 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA:	19-726
Compound:	Zoladex® (goserelin acetate implant) 3.6 mg Depot
Submission Date:	April 8, 1997 (Supplement No. 022)
Sponsor:	Zeneca Pharmaceuticals
Type of Submission:	Labeling Supplement
Reviewer:	K. Gary Barnette, Ph.D.

Summary:
On December 29, 1989 Zoladex (goserelin acetate implant) 3.6 mg Depot was approved for the indication of palliative treatment of advanced prostate cancer. Subsequently, this product was approved for treatment of endometriosis and breast cancer on February 2, 1993 and December 18, 1995, respectively.

On April 8, 1997 the sponsor submitted supplement 022 to NDA 19-726 to propose the addition of data to the product label that proposes a benefit of "add-back" hormonal replacement therapy for the treatment of endometriosis in the menopausal effects and osteoporotic effects associated with administration of Zoladex 3.6 mg Depot.

Recommendation:
The proposed product labeling for Zoladex (goserelin acetate implant 3.6 mg Depot, submitted to NDA 19-726 on April 8, 1998 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII). It should be noted that the sponsor does not propose any changes in the **Pharmacokinetic** subsection (Absorption, Distribution, Metabolism, Excretion, Special Populations or Drug-Drug Interactions) of the **CLINICAL PHARMACOLOGY** section of the product label. Therefore, OCPB/DPEII has no further comment.

/S/ 4/8/98

K. Gary Barnette, Ph.D.
Division Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 4/8/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 4/8/98

cc: NDA 19-726, HFD-580, HFD-580 (Safran, Dorantes), HFD-870 (M.Chen 13B-17, Dorantes, Barnette), Drug file (Barbara Murphy).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S22

ADMINISTRATIVE DOCUMENTS

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Group Leader's Memo

No Group Leader's memo will be prepared; /S/ 4/9/15

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Safety Update Review

Included in Medical Officer review dated 3/9/98.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Pharmacology Review

No pharmacology review is required.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Chemistry Review

No Chemistry Review is required.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Microbiology Review

No microbiology review is required.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Statistical Review

No statistical review is required.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

Advertising Material

No advertising material has been submitted.

NDA 19-726/S-022
Zoladex (goserelin acetate implant), 3.6 mg

DSI Audit of Clinical Studies

The reviewing medical officer indicated no DSI audit is required.

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-5437

ZOLADEX® (goserelin acetate implant) 3.6 mg
NDA 19-726

ITEM 13: Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

Certification

Pursuant to 21 CFR Section 314.53(d)(ii), Zeneca Limited, through its agent Zeneca Pharmaceuticals, A Business Unit of Zeneca Inc., certifies that US Patent No. 4,100,274; US Patent No. 4,767,628; and US Patent No. 5,366,734, information relative to each of which has been submitted previously, claim the formulation, composition and/or method of use of ZOLADEX® (goserelin acetate implant) 3.6 mg which is the subject of this supplemental new drug application.

Richard A. Elder

RICHARD A. ELDER
CHIEF IP COUNSEL
PHARMACEUTICALS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

DA/BLA # 19-726 Supplement # 22 Circle one (SE1) SE2 SE3 SE4 SE5 SE6

HFD-580 Trade and generic names/dosage form: ZOLADEX (goserelin acetate implant) 3.6 mg Action: (AP) AE NA

Applicant ZENECA Therapeutic Class 35

Indication(s) previously approved palliative treatment of advanced carcinoma of the prostate; management of endometriosis
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___ N/A
Proposed indication in this application Same as above

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ PROJECT MANAGER 4/7/98
Signature of Preparer and Title Date

Orig NDA/BLA # 19-726
HFD-580 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

ZENECA
Pharmaceuticals
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1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437
Telephone (302) 886-2132
Fax (302) 886-2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

APR 8 1997

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Labeling Supplement - Hormone Replacement Therapy

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under Section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.
(302) 886-2132
(302) 886-2822 (fax)

WJK/KFD/lmc

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