CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20011/S14

MEDICAL REVIEW(S)

MEDICAL REVIEW
NDA 20-011/S-014

APR 8 1998

1. **Resume**

This supplemental NDA, based on Amendment 122 to IND and specified as an "Efficacy Supplement for Prior Approval", is a proposal to add to the ADVERSE REACTIONS, *Changes in Bone Density*, Section of the label, reference to results of an unpublished study which appears to demonstrate that three "add-back" regimes, when used with the subject drug given for endometriosis, act to counteract the osteoporotic effects and menopausal symptoms induced by the subject drug, without reducing its favorable effects. It is recommended that the use of the various forms of "add-back" therapy described in this review, 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.

2. **General information**

2.1. **Medical Officer's review**

2.1.1. **NDA:** 20-011/S-014

2.1.2. **Submission received:** 23 September 1997

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

2.2 **Drug names**

2.2.1. **Generic name:**
Leuprolide acetate for depot suspension

2.2.2. **Trade name:**
Lupron Depot 3.75 mg

2.3 **Sponsor:**
Tap Holdings Inc.
Deerfield IL

2.4 **Pharmacological category:**
Gonadotropin-releasing hormone agonist

2.5 **Approved indications**

2.5.1. Prostatic carcinoma

2.5.2. Endometriosis
[**NOTE**: this supplement relates only to labeling for the endometriosis indication.]

2.5.3. Anemia associated with leiomyomata uteri

2.5.4. Central precocious puberty

2.6. **NDA drug classification:** S

2.7. **Related drugs**

Other drugs in this class include **goserelin acetate** (approved for the treatment of endometriosis, advanced breast cancer, and prostatic cancer), **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. Documents relating to prior discussions with Agency concerning this submission, reviewed in Section 8.

7.3. NDA 20-708

This NDA, a companion to the subject NDA, requests a similar label change for the 3 month formulation of leuprolide, termed "Lupron Depot-3 month 11.25 mg". The review for this NDA is essentially the same as this review.

7.4. NDA 19-726/S-022

This supplement was a request to add to the label of another GnRH-a drug the results of a study of another "add-back" therapy regimen.

7.5. 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.

7.6. 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.

7.7. 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".

7.8. 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.

7.9. 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, <u>the information provided strongly supports additional studies in the area</u>.." (emphasis added)

7.10. 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.."

7.11. 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)

7.12. 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.

7.13. 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-</u>

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". (emphasis added) [**NOTE**: see **Appendix 1** for a copy of this useful review.]

7.14. 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".

7.15. 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.

7.16. 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".

7.17. 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.

7.18. 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.

7.19. 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 the review pf NDA 19-726/S-022.

8. **Review of documented contacts between the Agency and the sponsor concerning this application**

09.09.93. Protocol 92-878 (the study on which this submission is based) was submitted to the Agency as Amendment 122 to IND [**NOTE**: No Agency review of this protocol can be found except for a "Final Safety Summary", dated 01.26.96. There appears to have been no comprehensive discussion with the sponsor of the issues related to "add-back" therapy raised in this review.]

05.22.96. In a letter to HFD-510 the sponsor asked for comments concerning the "preliminary results of Study M 92-0878" prior to formal submission of the application; the letter was allegedly "submitted as recommended by Dr. Rarick on the phone on May 3, 1996".

08.14.96. **In her response to the letter, Dr. Rarick, then Acting Director of HFD-580, told the sponsor that such a development "should be...in accordance with...currently available**

guidelines", and must "..determine the lowest effective dose of estrogen necessary to prevent bone mineral density (BMD) loss; and .. determine if the use of a progestin is necessary to prevent endometrial hyperplasia, and, if so, the lowest effective dose of the chosen progestin." Dr. Rarick also "strongly" suggested a meeting with the Division.

10.03.96. Without waiting for the suggested meeting, the sponsor submitted an amendment to NDA (S-012), noting that Dr. Rarick's comments didn't apply since "the intent of add-back therapy is temporary hormonal add-back for Endometriosis patients receiving Lupron Depot 3.75 mg. This is different from Hormone Replacement Therapy of Postmenopausal Women...and therefore, we believe that the guidelines mentioned in your letter of August 14, 1996 are not appropriate".

10.18.96. In a meeting between the Division and the sponsor (not attended by this reviewer), the sponsor reviewed the intent of the current application, namely to revise the label to include details of the study, and to extend the use of the agonist from 6 months to a year.

The Division made the following points, among others, at the meeting:

- "to extend the duration of use of any product and/or add specific additional therapy to the label, each company must strictly adhere to the regulatory framework for developing a new product/indication".
- "NET may be adequate, based on the results of the above study; if TAP wants to pursue the current proposal, they would need to justify their dose and regimen selection".
- "one possibility is to use a form of class labeling..for example **'many clinician's (sic) believe that the use of "add-back" therapy minimizes the amount of bone loss associated with the administration of GnRH agonists; however the optimal drugs, dose and duration have not been established..and further clarification of the definition of "add-back" is necessary'."** (emphasis added)

02.06.97. The supplement (S-012) was filed, apparently without further discussions with the Division.

04.04.97. Dr. Rarick wrote the sponsor that the Division refused to file the application because "no adequate dose ranging studies have been performed" and "because progestins have not been previously found to be safe and effective for prevention of bone loss, the resulting number of evaluable patients is insufficient to draw adequate conclusions.."

06.17.97 The "decisions reached" at a meeting with the sponsor were:

- o "this study will not support the extended use of Lupron. Because progestins have not been previously shown to prevent bone loss, a study replicating the finding is necessary."
- o "TAP had two options". The first is "to submit an efficacy supplement with their current data", the results of which may be placed in the label, but the duration of use must remain 6 months and "additional language that the optimum dose and treatment regimen have not been established will be required". The second option is to undertake a more highly powered study in an attempt to extend the use of the agonist beyond 6 months. [**NOTE**: This reviewer argues that the first option is not acceptable.]

08.18.97. The sponsor was present at a meeting of the Agency's "Refuse to File Review Committee", when the issues cited above were discussed.

09.23.97 This submission was received.

9. **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.

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

9.1. **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..." A larger study, as yet unpublished, of NET 5 mg/d as "add-back", is the subject of the review.

9.2. **"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 the review of NDA 19-726/S-022.

9.3. **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(7.14.) and Surrey(7.15.).

10. **Review of the submitted study**

INTRODUCTION

This study, entitled "**Combination Lupron depot-hormonal add-back in the management of endometriosis**", was a randomized, double-blinded, parallel-group trial in a total of 201 subjects with endometriosis, all who received Lupron Depot (LD) 3.75 mg each month for 12 months. The study, conducted in 26 American investigative sites, was designed to ascertain the ability of the three "add-back" regimes to ameliorate the bone loss and menopausal symptoms induced by Lupron given for the treatment of endometriosis, without reducing the efficacy of the treatment. The study design is provided in **Appendix 2**.

Patient selection and details of the study are provided in **Appendix 3**. All subjects "were required to have

moderate or severe pelvic pain (not related to menstruation) or moderate or severe deep dyspareunia with pelvic pain or moderate or severe dysmenorrhea with pelvic pain". All fertile subjects were to use barrier contraception during the study if they were fertile. **Appendix 4** shows the study's time-line; subjects were exposed to one of the 4 randomized regimens for 52 weeks. The time line displays the various examinations and laboratory tests that were done during the study and the time at which they were done.

EFFICACY

According to the sponsor, "Efficacy was evaluated based on improvement of disease symptoms.". **Appendix 5** displays 5 figures which compare the subjective and objective findings relating to efficacy. The subjective findings are "dysmenorrhea", "pelvic pain", and "deep dyspareunia"; the objective findings are "pelvic tenderness at each visit" and "pelvic induration..at each visit". The figures support the sponsor's claim that none of the 3 "add-back" regimens significantly reduced the efficacy of Lupron-Depot alone, although it appears that the regimens containing CEE may be slightly less effective that NET alone, and that the higher CEE dose regimen is further less effective. These findings appear to be consistent with the serum estradiol levels, displayed in **Appendix 6,** which demonstrate the apparently direct correlation between estradiol levels and the amount of CEE provided.

SAFETY

According to the sponsor, "Safety evaluations included adverse events, laboratory tests, and analysis of bone mineral density changes". Clearly the sponsor is most interested in bone loss; this is the finding they wish to provide in the label, as shown in **Appendix 7**. These findings suggest that the "add-back" regimens provided appear to prevent bone loss, but, as argued below, it would be inappropriate to permit including reference to these specific regimens in the label.

Appendix 8, which displays the distribution of various symptoms and signs during treatment, demonstrates a reduction in vasomotor symptoms with all 3 "add-back" regimens. **Appendix 9**, the summary table of "Clinical Laboratory Parameters", is unacceptably non-specific; however, the sponsor does conclude.."**With the possible exception of lipid changes**, there were no clinically

significant adverse trends associated with add-back therapy". [**NOTE**: As argued below, this study is similar to other studies of various "add-back" regimens in failing to adequately address blood lipid studies and other surrogates of cardiovascular disease.

Finally, **Appendix 10** displays the "Total Exclusions" and the number of "Evaluable" subjects. The views of the Biometrics Team concerning the impact of these findings on the significance of the study are, of course, critical, but it seems clear that the high drop-out rates seriously compromise the conclusions that may be drawn.

DEFICIENCIES

Although, as noted above, all 3 "add-back" 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.
- The number of evaluable subjects is too small to permit meaningful conclusions; the drop out rate was excessively high.
- None of the 3 regimens employed are approved for the prevention of vasomotor symptoms and bone loss in menopausal women.
- There was no dose-finding.
- Since all three "add-back" regimens had somewhat similar favorable effects, permitting this specific study to appear in labeling would not provide adequate guidance to clinicians and patients.

In conclusion, in the opinion of this reviewer, the Division Director's letter to the sponsor dated 4 April 1997 should remain the operative Division position concerning the adequacy of this study, namely:

- "no adequate dose ranging studies have been performed", and
- "the number of evaluable patients is insufficient to draw adequate conclusions on the safety and

efficacy of this regimen for the intended indication".

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

The findings cited in Sections 8 and 10 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. Also, this reviewer finds the very term "add-back" therapy suspect because the term implies that the treatment will result in reestablishment of normal conditions made abnormal by the agonist. More research is certainly required. For example, this study repeats the error of studies of other "add-back" regimens in not studying lipids and clotting factors, surrogates of possible cardiovascular disease.

Concerning the 2 "HRT" regimens employed in this study, 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. For example, this study repeats the error of studies of other "add-back" regimens in not studying in sufficient detail the effects of these various drug combinations on such parameters as 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 so-called "HRT" wasn't approved until a sponsor undertook appropriate and fully-compliant studies. A similar,

more deliberate, approach, appears 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 specific regimen of "HRT" were to become codified into practice through 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 a supplements to NDAs 19-726, in which the sponsor requests providing details of 2 "HRT" regimens as "add-back" regimen to the goserelin, are approved as requested.

12. **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**:

13. **Recommendations**

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

13.2. 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 Officer

cc: IND/NDA Arch
HFD-580/Rarick/Jolson/Corfman//wpfiles\20011.nda

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Attachment 1.1.

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

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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 de- -e (of up to 8.2%) in lumbar bone density, a p. enon which may not be entirely reversible 6 months afte: uiscontinuation 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 not flush. The concurrent or non-concurrent use of non-steroid 'add-back' regimens will also most likely constitute a major component of future studies.

Key words: add-back paradigms/gonadotrophin-releasing h

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

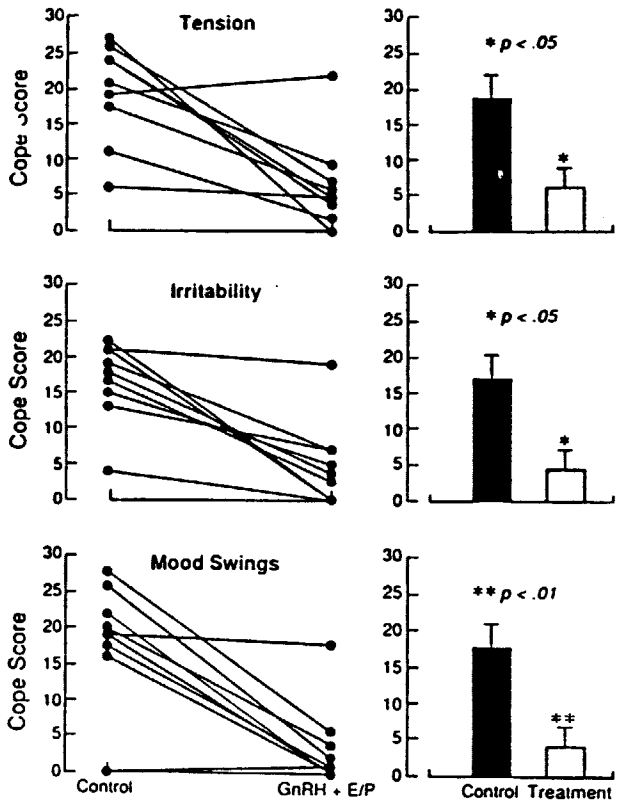

Fig. 1. Left panels, total calendar of pre-menstrual experiences (COPE) scores for tension, irritability, and mood swings for individual subjects during the luteal phase during months in which subjects were administered gonadotrophin-releasing hormone agonist (GnRHa) daily in addition to conjugated equine oestrogen (CEE) on days 1–25 and medroxyprogesterone acetate (MPA) on days 15–25 (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;

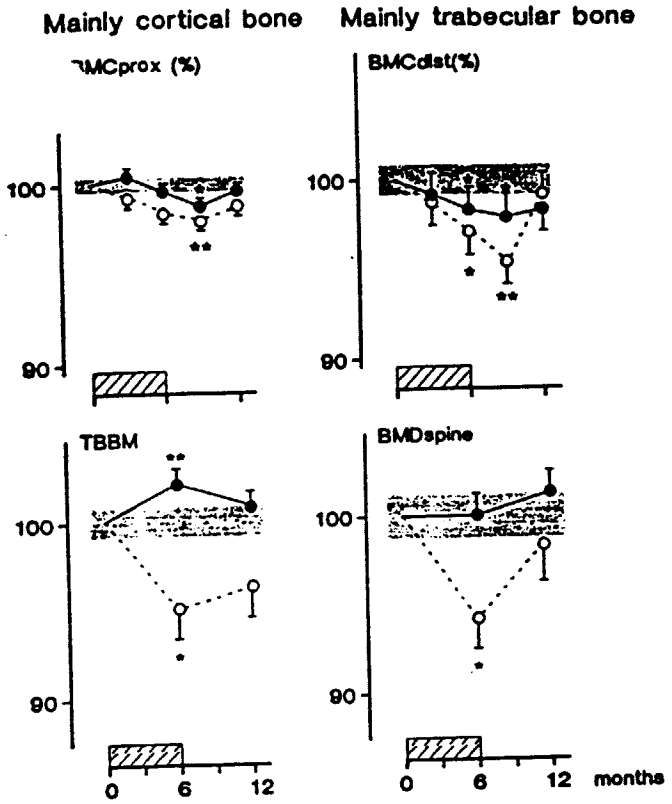

Fig. 2. Mean (±SEM) changes in bone mineral (percentage) during treatment and after withdrawal in the groups treated with nafarelin plus notethindrone (NET; solid circles) and nafarelin alone circles). The grey bars indicate the variation in changes 1 year in the control group (mean ± average SEM). *, $P < 0.05$; **, $P < 0.01$ (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).

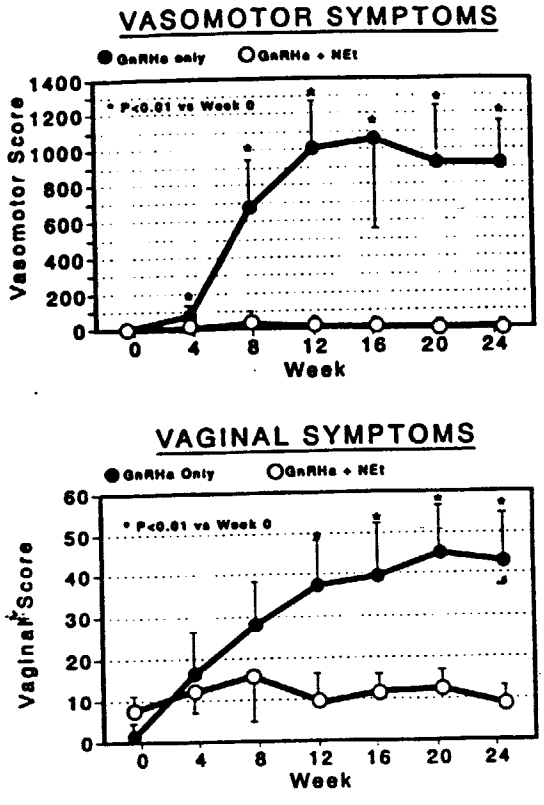

Fig. 3. Impact of a progestin (norethindrone)-only 'add-back' regimen on vasomotor symptoms and vaginal symptoms. Reproduced with permission from Surrey and Judd (1992).

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 of nafarelin/NET (Figure 2) or histrelin/MPA proved fully effective 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 than 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

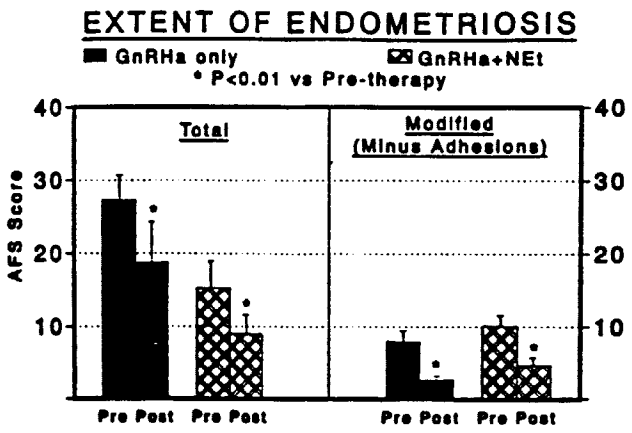

Fig. 4. Impact of a progestin (norethindrone)-only 'add-back' regimen on the extent of endometriosis as assessed by the American Fertility Society score. Reproduced with permission from Surrey and Judd (1992).

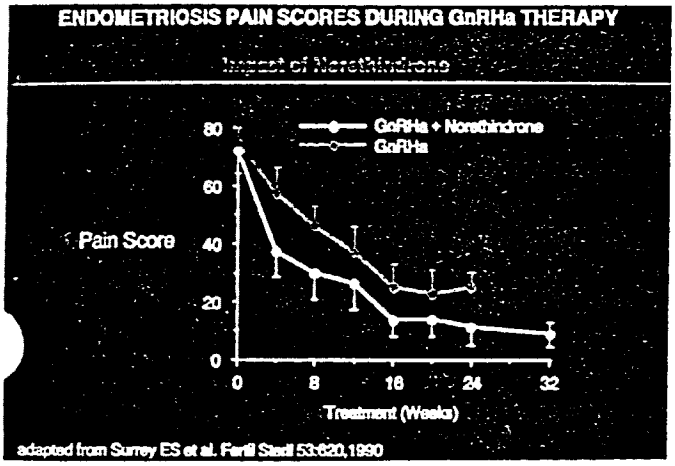

Fig. 5. Impact of a progestin (norethindrone)-only 'add-back' regimen on the pain score associated with symptomatic endometriosis. Adapted from Surrey *et al.* (1990).

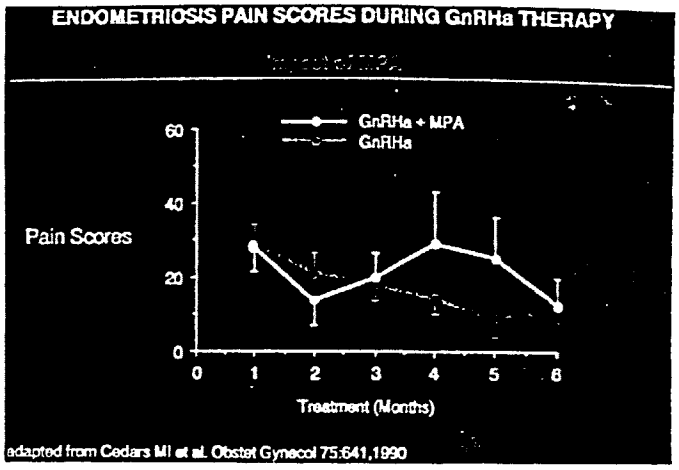

Fig. 6. Impact of progestin (MPA)-only 'add-back' regimen on the pain score associated with symptomatic endometriosis. Adapted from Cedars *et al.* (1990).

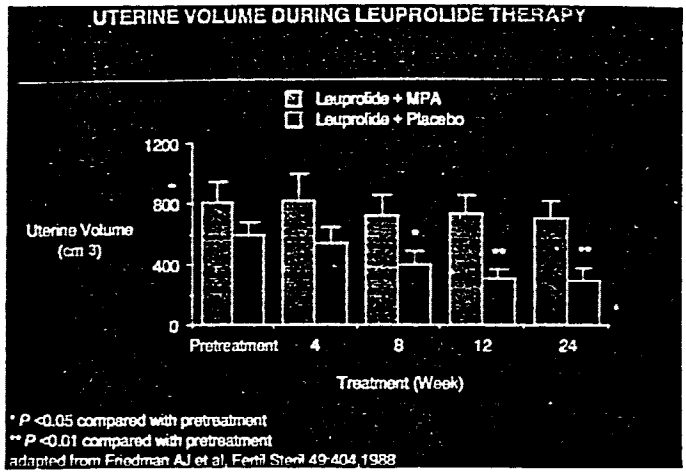

Fig. 7. Effect of concurrent progestin (MPA)-only 'add-back' on the ability of leuprolide to reduce the sonographically monitored uterine volume. Adapted from Friedman *et al.* (1988).

(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

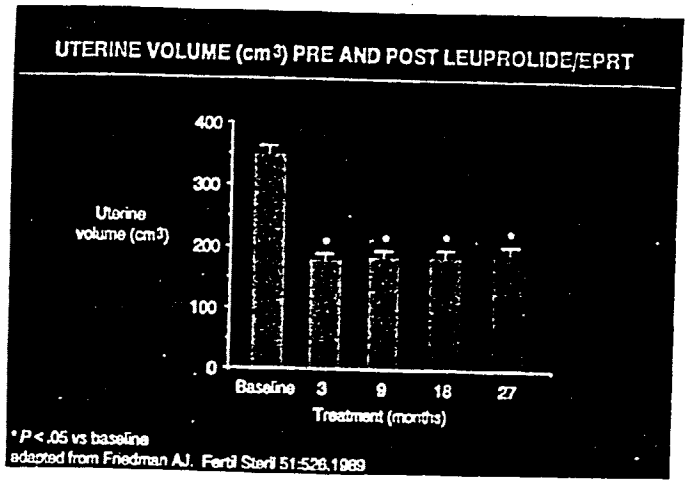

Fig. 9. Impact of a non-concurrent oestrogen/progestin 'add-back' regimen on sonographically monitored uterine volume. Adapted from Friedman (1989).

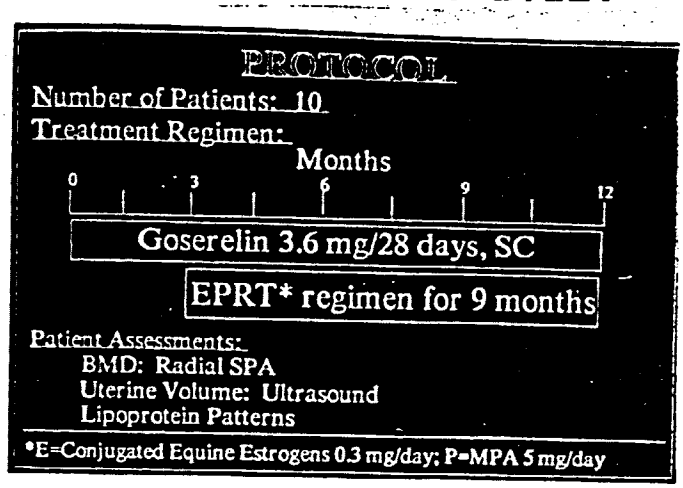

Fig. 10. Protocol of a non-concurrent oestrogen/progestin 'add-back' regimen designed to treat uterine fibroids. Adapted from Maheux *et al.* (1991).

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

	Bone density (g/cm^3)	
	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

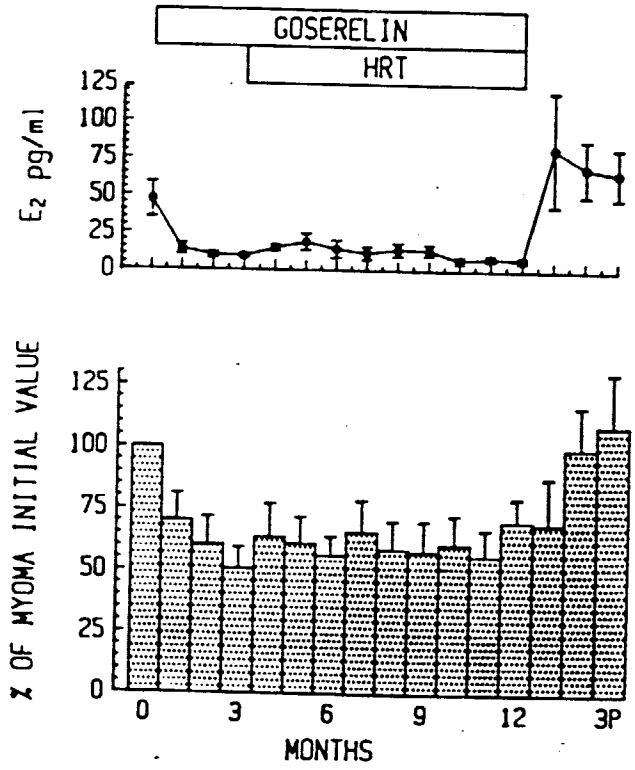

Fig. 11. Impact of an oestrogen/progestin 'add-back' regimen on circulating oestradiol (E_2) concentrations or on sonographically monitored volume (% of myoma initial value). Reproduced with permission from Maheux *et al.* (1991).

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 lupron every 4 weeks for 12 weeks, during which time randomization 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

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MEDICAL REVIEW
NDA 20-708/S-003

APR 8 1998

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Resume

This **"Efficacy Supplement for Prior Approval"**, is a proposal from Tap Holding, Inc. to make the same changes in the label of this drug, **Lupron Depot-3 Month 11.25 mg,** as were requested in NDA 20-011/S-014 to be made for **Lupron Depot 3.75 mg**, based on a study done with the later drug.

Insofar as earlier this year the Division approved a supplement to this NDA requesting approval for the treatment of endometriosis and fibroids based on pharmacological evidence that the drug levels for the monthly product given for 3 months were essentially the same as the drug levels for this 3-month product, the review and recommendations for this application are the same as the review and recommendations for NDA 20-011/S-014.

Recommendations

1. It is recommended that the submission be approved, but that the label change be limited as specified in Section 12 of the review of NDA 20-011/S-014.

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 Officer
17 December 1997

cc: IND/NDA Arch
HFD-580/Rarick/Jolson/Corfman//wpfiles\20708.nda

MAR 2 1998

Medical Officer Review of Safety Update

NDA: 20-011 Amendment dated January 22, 1998

Sponsor: Tap Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield IL 60015

Received: January 23,1998

Date Review Completed: February 19,1998

Drug: Lupron Depot ® (Leuprolide acetate for depot suspension) and Aygestin® (norethindrone acetate)

Proposed indication: Management of endometriosis with addback progestin to prevent bone loss.

Dosage Form: Lupron depot 3.75 mg, Aygestin (Norethindrone acetate) 5 mg.

Route of administration: Intramuscular for Lupron depot
Oral for Norethindrone acetate

Background: *The purpose of this submission is to update the clinical activity with Lupron® related to supplement S-014.*. This six volume submission contains the safety data from the follow-up period of clinical study M92-878 entitled "Combination Lupron depot-hormonal add-back in the management of endometriosis" which is submitted for review in support of approval of S-014.

Summary of Study Design:

Two hundred and one patients were assigned to one of four treatment groups: Group A (n=51) received placebo for the estrogen and pla-

cebo for the progestin, group B(n=55) received 5mg norethindrone acetate and placebo for the estrogen, group C (n=47) received 5mg norethindrone acetate (Aygestin®) and 0.625 mg conjugated estrogen (Premarin®), and group D (n=48) received 5 mg norethindrone acetate (Aygestin®) and 1.25 mg conjugated estrogen (Premarin®). Efficacy is based on symptom improvement (relief of pain) and physical exam. Safety evaluation included assessment of bone mineral density and lipids.

Results of Study:

Clinical Results:

Relief of pain: The primary efficacy outcome was improvement in pain variables evaluated on the four-point scale. The pain variables were dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and induration. Significant decreases from baseline in all pain scores were seen in both the Lupron-only group and the Lupron-progestin group. There were only two significant differences between the Lupron-only group and the Lupron-progestin group for any pain score at any of the visits. These two exceptions include a greater decrease from baseline in the Lupron progestin group for deep dyspareunia at Week 4 and pelvic induration at Week 40.

Dysmenorrhea: Statistically significant within-group mean decreases from baseline for dysmenorrhea occurred in both groups at all visits. The were no statistically significant between group differences.

Deep Dyspareunia: There was no statistically significant difference between the treatment groups in mean change from baseline in deep dyspareunia averaged over the treatment period. Both treatment groups showed statistically significant within-group decreases from baseline.

Bone mineral density: Bone mineral density was measured during the treatment period at week 24 and at week 52 (final treatment scan) and during the post-treatment period at Months 8, 12, 16, 20 and 24. Bone mineral density was assessed by measurement of the whole vertebral body (L1-L4) with machines. Results are presented in Table 1.

Table 1. Mean percent change in bone mineral density.

	Lupron only	Lupron/Aygestin	Lupron/Aygestin 0.625 CE	Lupron/Aygestin 1.25 CE
	mean % change	mean % change	mean % change	mean % change
Treatment period				
Final Scan for patients with Follow-up data	-5.52 (n=23)	-1.23(n=27)	-0.23(n=27)	0.58(n=23)
Post-Treatment period				
Month 8	-3.45(n=19)	-0.83(n=23)	0.17(n=24)	0.70(n=23)
Month 12	-2.48(n=16)	-0.72(n=12)	0.79(n=14)	0.52(n=14)
Month 16	-1.91(n=9)	-0.03(n=7)	1.18(n=14)	2.30(n=10)
Month 20	-1.89(n=3)	0.06(n=7)	0.34(n=5)	1.50(n=5)
Month 24	-2.35(n=3)	1.58(n=4)	1.20(n=4)	-0.81(n=2)
Final	-2.09(n=23)	-0.65(n=23)	0.96(n=27)	1.00(n=24)

The Lupron® only group had a statistically significant mean decrease from baseline at the Final Visit during treatment, at Months 8 and 12, and at the Final Visit during follow-up. Both groups treated with conjugated estrogen had a significant mean increase from baseline at the Final Visit during follow-up. All three add-back groups had a statistically significantly different mean bone loss compared to the Lupron only group at the Final Visit.

Safety related to bone mineral density: During the treatment period, four patients had exceptional decreases in bone mineral density. One patient in the Lupron® only group was discontinued from treatment with a bone mineral density that decreased by 8.3% at week 24. One patient in the Lupron® only group had a BMD loss of 10.4% at week 52, she did not have follow up scans because she was pregnant three months into the follow-up phase. One patient in the Lupron® only group had a BMD loss of 11.7% at week 52. One patient in the Lupron®/1.25 mg conjugated estrogen group had bone loss of 12.5% at week 52. Follow-up bone mineral density evaluation in the three nonpregnant patients with noteworthy bone loss showed improvement in bone mineral density after discontinuing active therapy.

Of the 42 patients in the Lupron with progestin group who underwent evaluation with scans at final treatment visit, 7 had more than a -3% change from baseline. The percent change in the 7 patients with more than 3% loss in bone mineral density at final visit were -4.7%, -8.0%, -4.9%, -4.7%, -3.6%, -5.1%,and -3.3%. (data tabulated from Vol. 1 appendix A-4 page 171-176 of the submission.) All but one of the patients who had post treatment scans showed improvement in bone mineral density from final treatment scan to their last follow-up scan. The one patient who did not show improvement had a final treatment scan showing a 3.3% decline in bone density, the only follow-up scan that patient had was at 8 months post treatment that yielded a 3.4% decline in bone density.

Reviewer's comments: No patients in the Lupron progestin group had exceptional bone loss(>8%) during this trial. It is encouraging that 85% (6 of 7) patients in the

Lupron progestin group with moderate bone loss (>3%) during active treatment had improvement in bone density during post-treatment follow-up.

Return of menses: Menses was defined as bleeding for three or more consecutive days requiring the use of sanitary products. Suppression of menses was defined as no menses for at least 60 consecutive days during treatment, regardless of whether any bleeding occurred thereafter. Treatment period menses suppression was between 94% to 100% for all treatment groups. Median time to first menses post-treatment was 48 to 69 days for all treatment groups.

Lipids:
Lipid profiles were evaluated at baseline Week 52 (end of Treatment) and at each follow up visit beginning at month 8. Results comparing lipids at baseline and at Week 52 are summarized in Table 2 .

Table 2 (from Integrated summary of safety)
Mean Serum Lipid Values at Baseline and Week 52

	LD-Only	LD + NET
Total Cholesterol (mg/dl)		
Baseline	168.0 ± 6.3	176.8 ± 5.7
Week 52	187.8 ± 4.8*	177.3 ± 4.4
HDL Cholesterol (mg/dl)		
Baseline	49.1 ± 2.9	51.2 ± 2.6
Week 52	51.6 ± 1.9	42.0 ± 1.8*
LDL Cholesterol (mg/dl)		
Baseline	95.5 ± 5.5	101.8 ± 5.0
Week 52	110.1 ± 4.8*	110.3 ± 4.4*
LDL/HDL Ratio		
Baseline	2.1 ± 0.2	2.1 ± 0.2
Week 52	2.3 ± 0.2	2.8 ± 0.2*

* Statistically significantly different from baseline.
Cross-reference: End-of-Text Table 14 and Appendix A.14.submission S-012

By the final no treatment follow up visit, 100% of the lipid values in the Lupron progestin group were normal.

Adverse events:
The most frequently reported adverse event in both the Lupron alone and the Lupron progestin groups was hot flashes. Other frequently reported adverse events noted in both groups include headaches, insomnia, nausea, asthenia and emotional lability.
Table 3 reports the adverse events noted in the study prior to this safety update.

Table 3. Frequently Reported Adverse Events Prior to Safety Update Which Were Related or May Have Been Related to Study Drug

	LD-Only		LD + NET	
COSTART Term	N	(%)	N	(%)
Any Symptom/Sign	50	(98)	53	(96)
Hot Flashes	50	(98)	47	(85)*
Headache	35	(69)	30	(55)
Insomnia	16	(31)	7	(13)*
Nausea	13	(25)	13	(24)
Asthenia	11	(22)	9	(16)
Emotional Lability	11	(22)	11	(20)
Vaginitis	11	(22)	9	(16)
Pain	10	(20)	13	(24)
Depression	8	(16)	5	(9)
Breast Pain	5	(10)	8	(15)

*Significantly less than the LD-only group.

Adverse events reported in the follow-up period were similar in frequency to those reported during active treatment. Frequent adverse events newly reported in the safety update are displayed in Table 4.

Table 4. Frequent Newly Reported Adverse Events Which Were Related or May Have Been Related to Study Drug

	LD-Only		LD + NET	
COSTART Term	N	(%)	N	(%)
Hot Flashes	0	(N/A)	1	(17)
Headache	2	(25)	0	(0)
Pharyngitis	0	(0)	4	(16)
Nausea	0	(0)	3	(12)
Vaginitis	4	(14)	2	(29)
Pain	3	(20)	1	(4)
Breast Pain	0	(0)	4	(11)

modified from table page 019 Vol. 1 NDA 20-011,S-014 safety update

Depression: Depression was a relatively common significant adverse event. Evaluation of serum estradiol levels at baseline, Week 24, and Week 52 appeared comparable between all patients and those with depression within each treatment group. Table 5 shows mean estradiol levels in patients with depression at baseline, Week 24 and Week 52.

Table 5. Mean estradiol levels (pg./ml) in patients with depression and in all patients by treatment group.

	Baseline	Week 24	Week 52
all LD only patients	62.26(n=29)	14.56(n=29)	12.82(n=16)
depressed patients LD only	139.02(n=8)	11.14 (n=8)	8.7 (n=8)
all LD/NET patients	41.22(n=25)	9.05(n=25)	9.2(n=17)
depressed patients LD/NET	41(n=6)	5.8(n=5)	9.5(n=2)
all LD/NET/0.625 CE patients	53.05(n=26)	21.66(n=26)	17.23(n=17)
depressed patients LD/NET/0.625 CE	45.66(n=15)	18.50(n=13)	16.33(n=12)
all LD/NET/1.25 CE patients	39.04(n=22)	16.72(n=22)	33.08 (n=15)
depressed patients LD/NET/1.25 CE	36(n=10)	40.55(n=9)	28.57 (n=11)

Terminations due to adverse events:
The 32 terminations for adverse events were distributed among all four treatment groups. Most terminations were for abdominal pain and psychological issues (depression, personality disorders, mild anxiety and decreased libido). One patient developed ovarian cancer and another developed alopecia.
One patient (patient in the Lupron® only group terminated on day 455 post treatment as a result of renal calculus. Her bone density scan at 12 months post treatment revealed a +2.4% change in bone density from baseline to the 12 month follow-up visit. Serum calcium, serum phosphorus and uric acid levels were within normal limits at all evaluations (levels measured on treatment days-14, 170, 198, 366, 709)
Recommended regulatory action: In summary, this safety update supports the safety profile of Lupron® depot used with Aygestin®. The submitted data do not reveal any significant changes in the safety profile of Lupron® depot used with Aygestin®.

/S/

Julian Safran M.D.
Medical Officer HFD-580

Agree, but the data support the safety profile of Lupron when Aygestin and Lupron plus CEE + Aygestin.

3/2/98

cc. NDA-20011/Division File/ADunson/LRarick/KMeaker/JSafran