MTRAC
Midlands Therapeutics Review and Advisory Committee

VERDICT & SUMMARY

Gonadorelin analogues

For the treatment of endometriosis

Committee's Verdict: CATEGORY B **BNF: 6.7.2**

For treatment of endometriosis: The gonadorelin analogues (buserelin, goserelin, leuprorelin, nafarelin and triptorelin) are suitable for prescribing in primary care upon the advice of a specialist (or a primary care prescriber with a special interest in womens' health).

***Definition of Category B**: suitable for restricted prescribing under defined conditions*

A number of meta-analyses and additional randomised controlled trials (RCTs) found that the gonadorelin analogues (considered as a group) were generally as effective as other hormonal treatments including danazol, combined oral contraceptives and progestogens, in reducing subjective symptoms and objective measures, for up to six months. The evidence for efficacy compared with placebo was limited and conflicting. The place in therapy of the gonadorelins was considered to be low, primarily because of their adverse events, especially their effect on bone mineral density.

A Cochrane meta-analysis of 11 RCTs found that there was insufficient evidence to conclude that the use of hormonal suppression before or after surgery for endometriosis was associated with significant benefit. Such use is not recommended by guidelines from the Royal College of Obstetricians and Gynaecologists.

MTRAC reviewed this drug because of changes in practice in the use of these agents.

Licensed indications considered

Buserelin, goserelin, leuprorelin, nafarelin and triptorelin are licensed for the treatment of endometriosis.[1-5]

Background information

Endometriosis is a chronic condition in which functioning endometrial tissue is found outside the intra-uterine cavity. This ectopic tissue is oestrogen-dependent. The main manifestations are pelvic pain and infertility, although the condition can be asymptomatic. It is usually diagnosed by laparoscopy.

Buserelin, goserelin, leuprorelin, nafarelin and triptorelin are synthetic analogues of gonadotrophin-releasing hormone (GnRHas). These drugs are generally used to treat the symptoms of endometriosis if first-line agents (NSAIDs and oral contraceptives) fail to provide acceptable relief. The GnRHas, when taken by women, cause a drop in oestradiol to post-menopausal levels within three to four weeks of use. The GnRHas have been in use for over 13 years and are generally considered as a group with regard to efficacy and safety.

Clinical efficacy

Cochrane review

In 2000, a Cochrane review evaluated data from 17 multinational RCTs (total n = 2,065), for the efficacy of treatment of endometriosis.[6] All five GnRHas were included in the trials. The patients were pre-menopausal women (aged 18 to 50) with laparoscopically diagnosed endometriosis.

Comparators in the trials were danazol (14 trials), and one trial each using placebo, gestrinone, and a combined oral contraceptive. No trials were found that compared a GnRHa with surgery or with another GnRHa. Included trials continued treatment for three or six months.

Outcomes included pain scores (dysmenorrhoea, dyspareunia, pelvic pain) and rAFS (revised American Fertility Society) scores (an objective assessment including size and depth of invasion of endometriotic lesions, size of endometriotic cysts, and severity of adhesion formation). Most trials were small and of moderate quality.

Meta-analyses were done for the different groups based on the comparators. No differences were found for pain measures or rAFS scores between the groups taking GnRHas and any of the active comparators. In the placebo-controlled trial, leuprorelin was associated with greater reductions in pain scores and fewer withdrawals due to lack of efficacy.

Additional trials

A further seven RCTs evaluated GnRHas for endometriosis (n = 35 to 252).[7-14] Comparators were placebo,[8,11] a progestogen (lynestrenol),[12] "expectant management" (the meaning of which was not defined),[10] a different GnRH,[7,14] and danazol.[9] Treatment duration ranged from one month (one

placebo-controlled trial) to six months. Outcome measures included pain scores and rAFS scores.

Compared with placebo, leuprorelin therapy produced worsening of pain and quality of life during a one-month trial[11](covering the stimulatory phase of GnRHa action), but triptorelin produced greater improvement in pain and extent of endometriotic lesions after six months of treatment in another trial.[8] Leuprorelin therapy was more effective than lynestrenol in relieving subjective and objective markers of endometriosis,[12] and buserelin was more effective than "expectant management" in relieving pain.[10]

In the remaining three trials, there were no differences in efficacy between treatment with the GnRHas and the comparators, which were other GnRHas or danazol.[7,9,14]

Three more recently published RCTs were designed to assess the efficacy of a progestogen (either dienogest or depot medroxyprogesterone acetate) by comparing it with buserelin[15] or leuprolide.[16,17] Improvements in pain measures were found with all groups during the trial, compared with baseline. No differences were found between the GnRHas and comparator groups for pain measures, but there was less loss of bone mineral density with the progestogens than with the GnRHas.

Add-back therapy

In the Cochrane review,[6] five additional small trials compared GnRHa with GnRHa plus "add-back" therapy, in which either oestrogen alone or oestrogen plus progestogen was added to the GnRHa treatment to reduce adverse effects (total n = 225). These trials found similar efficacy between the treatment groups but a lower incidence of hot flushes in the groups with add-back therapy.

A later Cochrane review assessed RCTs of the effect of GnRHas on bone mineral density (BMD) compared with placebo in women with endometriosis, including the effect of add-back therapy.[18] In the meta-analysis of four trials for the effect of add-back therapy (total n = 298), GnRHa plus add-back therapy with oestrogen alone, or oestrogen plus progesterone, was associated with a higher absolute value for BMD at the lumbar spine than GnRHa alone, after six months of treatment (standardised mean difference: -0.49 [95% CI -0.77 to -0.21]). The significant difference was maintained at six and 12 months after treatment, but not after 24 months. Progesterone alone was not found to be protective.

Peri-operative use

A Cochrane review of 11 RCTs (total n = 955) has assessed the use of therapies for hormonal suppression before or after surgery for endometriosis.[19] The only trial of pre-operative use (n = 80) found a significant improvement in the rAFS score, but no difference between groups for adhesion scores. Pain was not measured. In the review, there was no benefit of post-surgical hormonal suppression on pain or pregnancy rates compared with surgery alone or surgery plus placebo. The reviewers concluded that there was insufficient evidence that peri-operative hormonal suppression was associated with a significant benefit for any of the outcomes measured.

In two additional RCTs, one of pre-operative use (n = 48), found benefit with goserelin in reducing the size of the endometrioma compared with no treatment prior to surgery.[20] Another, of post-surgical use (n = 133), found greater improvement in pain with leuprolide than with combined oral contraceptive.[21]

The Royal College of Obstetricians and Gynaecologists guidelines for the management of endometriosis (2006) concluded that there was insufficient evidence of effect on outcomes such as pain relief to justify preoperative or postoperative use of hormonal treatment.[22]

Adverse effects

The adverse events seen most commonly with the GnRHas in the trials were typical of the perimenopause, including hot flushes, insomnia, reduced libido, vaginal dryness and loss of bone mineral density. See the Summaries of Product Characteristics (SPC) for further details.[1-5]

Additional information

- The GnRHas are available as a nasal spray, implant or subcutaneous or intramuscular injection, administered every month or every three months.
- The current cost of six months' treatment with a GnRHa ranges from £334 to £525.

References

The references are listed on the next page

Manufacturers:Pharmacia, Sanofi Aventis, AstraZeneca, Takeda, Ipsen
WARNING: This sheet should be read in conjunction with the Summaries of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.
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NO RELEVANT GUIDANCE WAS AVAILABLE FROM NICE AT THE TIME OF ISSUE OF THIS VERDICT

VERDICT & SUMMARY REFERENCES
Gonadorelin analogues for the treatment of endometriosis

1. Synarel nasal spray. Pharmacia. 2007. http://www.medicines.org.uk/emc/ <accessed 3/2010>
2. Suprefact nasal spray. Sanofi Aventis. 2009. http://www.medicines.org.uk/emc/ <accessed 3/2010>
3. Zoladex 3.6 mg implant. AstraZeneca. 2009. http://www.medicines.org.uk/emc/ <accessed 3/2010>
4. Prostap SR. Takeda. 2009. http://www.medicines.org.uk/emc/ <accessed 3/2010>
5. Decapeptyl SR 3 mg. Ipsen. 2009. http://www.medicines.org.uk/emc/ <accessed 3/2010>
6. Prentice A, Deary AJ, Goldbeck-Wood S *et al*. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev* 2000;CD000346.
7. Agarwal SK, Hamrang C, Henzl MR *et al*. Nafarelin vs. leuprolide acetate depot for endometriosis. Changes in bone mineral density and vasomotor symptoms. Nafarelin Study Group. *J Reprod Med* 1997;**42:**413-23.
8. Bergqvist A, Bergh T, Hogstrom L *et al*. Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998;**69:**702-8.
9. Dawood M, Sellacy W, Dmowski W *et al*. A comparison of the efficacy and safety of buserelin *vs*. danazol in the treatment of endometriosis. *Current Concepts in Endometriosis* 1990;253-67.
10. Fedele L, Bianchi S, Bocciolone L *et al*. Buserelin acetate in the treatment of pelvic pain associated with minimal and mild endometriosis: a controlled study. *Fertil Steril* 1993;**59:**516-21.
11. Miller JD. Quantification of endometriosis-associated pain and quality of life during the stimulatory phase of gonadotropin-releasing hormone agonist therapy: a double-blind, randomized, placebo-controlled trial. *Am J Obstet Gynecol* 2000;**182:**1483-8.
12. Regidor PA, Regidor M, Schmidt M *et al*. Prospective randomized study comparing the GnRH-agonist leuprorelin acetate and the gestagen lynestrenol in the treatment of severe endometriosis. *Gynecol Endocrinol* 2001;**15:**202-9.
13. Zhao SZ, Kellerman LA, Francisco CA *et al*. Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. *J Reprod Med* 1999;**44:**1000-6.
14. Bergqvist A. A comparative study of the acceptability and effect of goserelin and nafarelin on endometriosis. *Gynecol Endocrinol* 2000;**14:**425-32.
15. Harada T, Momoeda M, Taketani Y *et al*. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis--a randomized, double-blind, multicenter, controlled trial. *Fertil Steril* 2009;**91:**675-81.
16. Schlaff WD, Carson SA, Luciano A *et al*. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. *Fertil Steril* 2006;**85:**314-25.
17. Strowitzki T, Marr J, Gerlinger C *et al*. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. *Hum Reprod* 2010;**25:**633-41.
18. Sagsveen M, Farmer JE, Prentice A *et al*. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. *Cochrane Database Syst Rev* 2003;CD001297.
19. Yap C, Furness S, Farquhar C. Pre and post operative medical therapy for endometriosis surgery. *Cochrane Database Syst Rev* 2004;CD003678.
20. Shaw R, Garry R, McMillan L *et al*. A prospective randomized open study comparing goserelin (Zoladex) plus surgery and surgery alone in the management of ovarian endometriomas. *Gynaecological Endoscopy* 2001;**2001:**151-7.
21. Zupi E, Marconi D, Sbracia M *et al*. Add-back therapy in the treatment of endometriosis-associated pain. *Fertil Steril* 2004;**82:**1303-8.
22. Royal College of Obstetricians and Gynecologists. The investigation and management of endometriosis. RCOG. 2006. http://www.rcog.org.uk/womens-health/clinical-guidance/investigation-and-management-endometriosis-green-top-24 <accessed 2/10>