



Goserelin

(Zoladex®)

For the treatment of prostate cancer

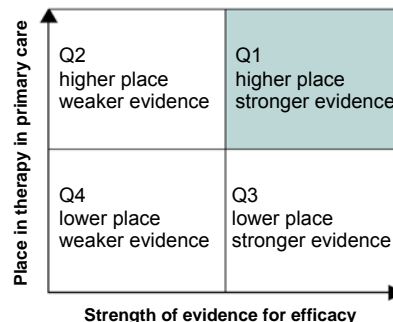
Committee's Verdict: **CATEGORY B (Q1)**

BNF: 8.3.4

Goserelin is suitable for prescribing in primary care upon advice from a specialist, with a shared care agreement.

Category B: suitable for restricted prescribing under defined conditions

Q1 rating: The strength of the clinical evidence for efficacy of goserelin was considered to be relatively strong for adjuvant use with radiotherapy, for localised and locally advanced prostate cancer. This was based on three randomised open-label trials of moderate quality showing clinically important positive effects on survival at five to ten years, compared with radiotherapy alone. There was also evidence for the use of goserelin plus flutamide as neoadjuvant to radiotherapy. Use for metastatic prostate cancer is supported by its effect on serum testosterone concentrations and over ten years of clinical experience; specific robust clinical evidence is lacking. As the LHRH agonist with the most exposure in clinical practice, goserelin has a high place in therapy.



The Q rating relates to the drug's position on the effectiveness indicator grid. The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.

MTRAC updated the review on this drug to include changes to the licensed indications and guidance from NICE.

Licensed indications

The indications for goserelin for the treatment of prostate cancer are:¹

- metastatic prostate cancer
- locally advanced prostate cancer, as an alternative to surgical castration
- as adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- as adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression

Background information

Prostate cancer is the most common cancer in men. The Office for National Statistics reported 117 new diagnoses per 100,000 men for 2005.² Although the mortality rate has been declining, this has been balanced by a rise in the incidence.

Localised prostate cancer in men at low risk is treated by watchful waiting or active surveillance. For metastatic prostate cancer, androgen deprivation (or withdrawal) therapy, either by orchidectomy or drug-induced castration, has been considered to be an effective treatment for over 60 years.³ Androgen

deprivation therapy is also used as adjunct therapy for patients undergoing radiotherapy or prostatectomy for high-risk localised or locally advanced prostate cancer.

Medical castration with luteinising hormone-releasing hormone (LHRH) agonists has increased substantially since the mid-1980s, primarily as an alternative to orchidectomy.³ These drugs lead to suppression of sex-hormone secretion. The two most commonly used LHRH agonists are goserelin and leuprorelin.

NICE guidance

In April 2008, the National Institute for Clinical Excellence (NICE) published a Clinical Guideline on prostate cancer.³ NICE recommended that for **metastatic prostate cancer**, bilateral orchidectomy should be offered as an alternative to continuous LHRH agonist therapy. For **localised and locally advanced prostate cancer**, adjuvant "hormonal therapy" [*type not specified*] was recommended for a minimum of two years in men receiving radical radiotherapy who have a Gleason score ≥ 8. Adjuvant "hormonal therapy" in addition to radical prostatectomy was not recommended other than in a clinical trial. For **locally advanced prostate cancer**, neoadjuvant and concurrent LHRH agonist therapy was recommended for three to six months in men receiving radical radiotherapy.

Clinical efficacy

Advanced prostate cancer

The use of goserelin in advanced prostate cancer appears to be based on evidence from mostly uncontrolled trials showing that goserelin reduced serum testosterone concentrations to near castration levels in over 90% of patients. Two trials reported that, when goserelin was compared with orchidectomy in the treatment of advanced prostate cancer, there was no difference in survival at six to 24 months.

The evidence used to support the NICE guidance on the use of LHRH agonists or "hormone therapy" for advanced prostate cancer was based on one meta-analysis of 21 RCTs (involving over 6,600 patients) comparing the effect of different treatments on survival: LHRH agonists (including four trials of goserelin and one of leuprorelin), anti-androgens, orchidectomy and diethylstilboestrol.⁴ No difference in overall survival was found between LHRH agonists and orchidectomy, at two years, based on two trials with goserelin and three with buserelin (another LHRH agonist). The hazard ratio for two-year mortality with LHRH agonists compared with orchidectomy was 1.26 [95% CI 0.95 to 1.36].

Localised and locally advanced prostate cancer

Trials assessing goserelin as adjuvant or neoadjuvant compared goserelin with radical radiotherapy alone.

Goserelin as adjuvant therapy. Three open-label studies (n = 415; 1,514; 945) compared goserelin as adjuvant to radiotherapy for five years^{5,6} or 10 years.⁷ An anti-androgen was given for the first month of adjuvant treatment in one study,⁵ and as neoadjuvant only in another study.⁶ Significant benefits were observed for overall survival (in two studies), disease-free survival, incidence of distant metastases, disease-specific mortality, and local progression, with goserelin compared with no adjuvant treatment.

No studies assessing goserelin use as adjuvant to prostatectomy were found.

Goserelin as neoadjuvant therapy. Two open-label, prospective, randomised trials (n = 456; 802) compared the effect of goserelin plus flutamide given for two to six months before and during radiotherapy with radiotherapy alone.^{8,9} In one study, at ten years, disease-specific mortality and the incidence of distant metastases were significantly different in favour of goserelin plus flutamide, but not overall mortality (43% vs. 34%).⁸ In the second study, the hazard ratios favoured goserelin plus flutamide significantly for local failure, biochemical (PSA) failure-free survival, disease-free survival and freedom from salvage treatment, at a median follow-up time of 5.9 years.⁹

Adverse events

In clinical trials, reported adverse events with hormone therapy included hot flushes, breast tenderness, decreased libido, asthenia, dyspnoea on exertion, depression and diarrhoea. Several retrospective studies of androgen deprivation therapy have reported a higher risk of cardiovascular disease, myocardial infarction, fractures and diabetes. For additional information on adverse events, refer to the Summary of Product Characteristics (SPC).¹

Additional information

- The recommended dose of goserelin is one 3.6 mg depot of goserelin injected subcutaneously into the anterior abdominal wall, every 28 days, or one depot of 10.8 mg injected every 12 weeks.
- At current prices, the cost of one year's treatment with goserelin 3.6 mg every 28 days is £1,097 and for 10.8 mg every 12 weeks is £1,159.

Key references (full list available upon request)

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4. Seidenfeld J, Samson DJ, Hasselblad V *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000;**132**:566-577.
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6. Hanks GE, Pajak TF, Porter A *et al.* Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cyoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;**21**:3972-3978.
7. Pilepich MV, Winter K, Lawton CA *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;**61**:1285-1290.
8. Roach M, III, Bae K, Speight J *et al.* Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;**26**:585-591.
9. Denham JW, Steigler A, Lamb DS *et al.* Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol* 2005;**6**:841-850.

Launch date: 1993

Manufacturer: AstraZeneca

PL 17901/0064, 0065

WARNING: This sheet should be read in conjunction with the Summary 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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Date: July 2008

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