



# VERDICT & SUMMARY

## Leuprorelin

(Prostap<sup>®</sup>)

For the treatment of prostate cancer

Committee's Verdict: **CATEGORY D**

BNF: 8.3.4

Leuprorelin cannot be recommended for prescribing because of inadequate evidence for clinical efficacy. MTRAC recognises the long established use of the LHRH agonists (mostly goserelin) for metastatic prostate cancer, based on their ability to suppress serum testosterone concentrations, clinical experience, and the positive effect of androgen deprivation therapy in general on survival, determined in a large meta-analysis. The assumption has been made that these agents are equally efficacious to each other and to orchidectomy. Evidence for clinical efficacy of leuprorelin is limited to two randomised open-label trials assessing the effect of leuprorelin plus flutamide as neoadjuvant before prostatectomy (an unlicensed indication) on histopathological and biochemical progression (PSA) of prostate cancer. Significant benefit was found, but because leuprorelin was combined with flutamide, and compared with no hormone treatment, the benefit could not be attributed to leuprorelin. The studies were considered to provide inadequate evidence for efficacy of leuprorelin for its licensed indications.

**Category D:** cannot be recommended for prescribing because of inadequate evidence for efficacy and/or safety

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

### Licensed indications

The indications for leuprorelin for the treatment of prostate cancer are:<sup>1</sup>

- metastatic prostate cancer
- locally advanced prostate cancer, as an alternative to surgical castration
- as an adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer
- as an 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup> These drugs lead to suppression of sex-hormone secretion. The two most commonly used are goserelin and leuprorelin; others are buserelin and triptorelin.

### NICE guidance

In April 2008, the National Institute for Clinical Excellence (NICE) published a Clinical Guideline on prostate cancer.<sup>3</sup> 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 for localised prostate cancer who have a Gleason score  $\geq 8$ . 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 leuprorelin in advanced prostate cancer appears to be based on evidence showing that leuprorelin reduced serum testosterone concentrations to near castration levels in over 90% of patients, in several uncontrolled trials<sup>4-6</sup> and in two comparative trials, one with goserelin<sup>7</sup> and one with triptorelin.<sup>8</sup> No comparative trials with orchidectomy were found for leuprorelin.

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.<sup>9</sup> 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.

### **Localised and locally advanced prostate cancer**

Two studies (n = 161; 287) compared leuprorelin combined with the anti-androgen flutamide, used as neoadjuvant therapy (unlicensed indication) before prostatectomy, with prostatectomy alone.<sup>10,11</sup> Significant benefit in the combined hormonal treatment arm was seen for histopathological disease progression,<sup>10</sup> incidence of capsule penetration, positive surgical margins (i.e. presence of tumour cells at the margin of surgically removed tissue) and of tumour at the urethral margin.<sup>11</sup> Survival outcomes were not used in these studies. One of the two studies reported that there was no difference in biochemical progression, as indicated by PSA concentrations, at five years.<sup>12</sup> Because the control group was not treated with hormonal therapy, the difference cannot be attributed to leuprorelin, only to the hormone combination.

No relevant studies using leuprorelin as adjuvant therapy were found.

### **Adverse effects**

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 (including LHRH agonists, anti-androgens and orchidectomy, or not specified) have reported a higher risk of cardiovascular disease or myocardial infarction,<sup>13,14</sup> fractures<sup>15,16</sup> and developing diabetes.<sup>17</sup> For additional information on adverse events, refer to the Summary of Product Characteristics (SPC).<sup>1</sup>

### **Additional information**

- The recommended dose of leuprorelin is 3.75 mg injected subcutaneously or intramuscularly every month, or 11.25 mg injected subcutaneously every three months.
- At current prices, the cost of one year's treatment with leuprorelin (either formulation) is £1,505.

### **References**

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Launch date: 1993

Manufacturer: Wyeth

PL 00011/0271, 0295

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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