Goserelin and psychiatric disorders in treatment of prostate cancer

Introduction
In the Netherlands several synthetic analogues of Luteinizing Hormone-Releasing Hormone (LH-RH) - also known as Gonadotropin-releasing Hormone (GnRH) - are approved for the treatment of prostate cancer. These GnRH receptor agonists such as goserelin, buserelin, and leuprorelin (leuprolide acetate) cause the inhibition of lutenizing hormone production during chronic administration. This in turn causes suppression of the synthesis of testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends.

Goserelin is indicated for the suppression of testosterone production in the treatment of metastasized prostate carcinoma, for adjuvant hormonal therapy to radiotherapeutical treatment of locally extended prostate carcinoma, for treatment of receptor positive metastasized mamma carcinoma in combination with tamoxifen in pre- and perimenopausal women, and for the management of endometriosis and uterine fibroids. It is also given before surgery for endometrial reduction [1]

Buserelin is indicated for the suppression of testosteron production in the treatment of metastasized prostate carcinoma[2]

Leuprorelin is indicated for the suppression of testosteron production in the treatment of metastasized prostate carcinoma, for the management of endometriosis and as pre-operative treatment of leiomyomata uteri and for the management of ideopathic central precocious puberty [3]

These indications imply that in the Netherlands goserelin and leuprorelin will be prescribed to both men and women and that buserelin will be prescribed to men only.

Reports
Until 20 May 2006, the Netherlands Pharmacovigilance Centre Lareb received 5 reports of a psychiatric disorder associated with the use of GnRH receptor agonists in male patients: one report associated with the use of buserelin and four reports associated with goserelin. We received no reports of psychiatric disorders associated with the use of leuprorelin in male patients.

The time to onset for buserelin in patient A was 7 months and varied from one week to 5 months for goserelin treated patients. Two patients required treatment with antidepressants or antipsychotics. Hormone levels (testosterone) were not reported in all reports. However, about patient A it was reported that he recovered from the depressive symptoms after withdrawal of buserelin but before the rise of his testosteron levels. Patient E was the only individual with a reported medical history of a psychiatric disorder (depression).
Table 1. reports of psychiatric disorders associated with the use of goserelin and buserelin by male patients.

<table>
<thead>
<tr>
<th>Patient, Sex, age</th>
<th>Dose</th>
<th>Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A M, 56</td>
<td>9.45 mg buserelin prostate carcinoma</td>
<td>not reported</td>
<td>depression, emotional lability</td>
<td>7 months, recovered (dechallenge positive)</td>
<td></td>
</tr>
<tr>
<td>B M, 67</td>
<td>10.8 mg goserelin prostate carcinoma</td>
<td>vitamin C, terphenadin, opticrom, finimal, lomusol nasal spray</td>
<td>emotional lability</td>
<td>1 week, not reported</td>
<td></td>
</tr>
<tr>
<td>C M, 63</td>
<td>10.8 mg goserelin prostate carcinoma</td>
<td>triamterene/hydrochlorothiazide, pindolol, cyproterone</td>
<td>insomnia, constipation</td>
<td>3 weeks not recovered after 4 months</td>
<td></td>
</tr>
<tr>
<td>D M, 74</td>
<td>10.8 mg goserelin prostate carcinoma</td>
<td>tamsulosin</td>
<td>depression, psychosis, sleep disorder, pruritus</td>
<td>not reported, not recovered (treated with mirtazapine and oxazepam)</td>
<td></td>
</tr>
<tr>
<td>E M, 80</td>
<td>10.8 mg goserelin prostate carcinoma</td>
<td>bicalutamide, clonidine</td>
<td>psychosis</td>
<td>5 months recovered (treated with haloperidol and oxazepam, next with olanzapine and oxazepam)</td>
<td></td>
</tr>
</tbody>
</table>

Other sources of information

SPC
Mood disorders, i.e. depressed feelings, are described in the SPC of goserelin, but specifically in relation to reduced estradiol levels in females[1]. In the SPC of buserelin nervousness, emotional lability, anxiety and depression (newly diagnosed or aggravated) are listed as rarely (0.01 – 0.1%) occurring adverse reactions [2]. Depression, insomnia, irritability are some of the psychiatric disorders listed as adverse reactions in men in the SPC of leuprorelin. In addition the same SPC of leuprorelin separately lists depression, emotional lability, insomnia, nervousness, anxiety and delusions as some of the psychiatric adverse reactions in women [3].

Literature
Declining male testosterone levels are associated with symptoms such as weakness, fatigue, decreased libido, depressive mood, lack of motivation and energy, lower psychological vitality, anxiety, irritability, insomnia, decreased work and sport performances, difficulty in concentrating, and memory impairment. [4]. Forty men with prostate cancer were treated with androgen blockade therapy (flutamide and leuprolide) which was clinically associated with increased scores in depression and anxiety tests [5]. However, it has been difficult to establish a therapeutic effect of testosterone substitution on the symptoms of depression [6].
### Prescription data

**Table 2. Total number of patients treated with GnRH receptor agonists in the Netherlands.**

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buserelin (<em>Suprefact</em>)</td>
<td>7.352</td>
<td>6.258</td>
<td>5.151</td>
<td>4.225</td>
<td>3.528</td>
</tr>
<tr>
<td>Leuprorelin (<em>Lucrin</em>)</td>
<td>7.575</td>
<td>8.039</td>
<td>8.497</td>
<td>7.864</td>
<td>8.279</td>
</tr>
</tbody>
</table>

Source: GIP/College voor zorgverzekeringen 2006 (http://www.gipdatabank.nl/)
Updated: 22-04-2006

### Discussion and conclusion

The exact mechanism by which sex hormones influence mood and other psychiatric disorders in men remains elusive. A factor that may be of influence in pharmacological castration is that compared to natural gonadorelin (LHRH) goserelin is 100 times as powerful and buserelin is 16 times as powerful [7].

Lareb received one report of depression in a man in association with treatment with buserelin and four reports of psychiatric disorders in men in association with treatment with goserelin, including psychosis and depression. Psychiatric adverse reactions are described in the SPC of goserelin, but specifically in relation to reduced estradiol levels in females. The association between GnRH receptor agonists and psychiatric adverse reactions in men is listed in the SPCs of buserelin and leuprorelin, the two other GnRH receptor agonists licensed for treatment of men in the Netherlands.

### References

7. Informatorium Medicamentorum 2006