When downregulation is achieved, superovulation (controlled ovarian stimulation) with gonadotrophin is commenced. The downregulation achieved with a depot agonist is more consistent suggesting that, in some cases, there may be an increased requirement for gonadotrophin. At the appropriate stage of follicular development, gonadotrophin is stopped and human chorionic gonadotrophin (hCG) is administered to induce ovulation. Treatment monitoring, oocyte retrieval and fertilisation techniques are performed according to the normal practice of the individual clinic.

No dosage adjustment is necessary for patients with renal impairment.

No dosage adjustment is necessary for patients with hepatic impairment.

No dosage adjustment is necessary in the elderly.

Endometriosis should be treated for a period of six months only, since at present there are no clinical data for longer treatment periods. Repeat courses should not be given due to concern about loss of bone mineral density. In patients receiving 'Zoladex' for the treatment of endometriosis, the addition of hormone replacement therapy (a daily oestrogenic agent and a progestogenic agent) has been shown to reduce bone mineral density loss and vasomotor symptoms.

For use in endometrial thinning; two depots to be administered 4 weeks apart, with surgery timed for between zero and two weeks after the second depot. For women who are anaemic as a result of uterine fibroids, 'Zoladex' 3.6 mg depot with supplementary iron may be given for up to three months before surgery.

'Zoladex' is not indicated for use in children.

For correct administration of 'Zoladex', see instructions on the instruction card.

Contra-indications
'Zoladex' should not be given to patients with a known hypersensitivity to the active substance, to

(goserelin)

Presentation
‘Zoladex’ is presented as a sterile, white to cream coloured cylindrical depot in which goserelin acetate (equivalent to 3.6 mg of goserelin) is dispersed in a biodegradable matrix of lactide-glycolide co-polymer. It is supplied as a single dose SafeSystem™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant.

Indications
I) Prostate cancer: ‘Zoladex’ is indicated in the management of prostate cancer suitable for hormonal manipulation.
II) Breast cancer: ‘Zoladex’ is indicated in the management of breast cancer in premenopausal and perimenopausal women suitable for hormonal manipulation.
III) Endometriosis: In the management of endometriosis, ‘Zoladex’ alleviates symptoms, including pain, and reduces the size and number of endometrial lesions.
IV) Endometrial thinning: ‘Zoladex’ is indicated for the prethinning of the uterine endometrium prior to endometrial ablation or resection.
V) Uterine fibroids: ‘In conjunction with iron therapy in the haematological improvement of anaemic patients with fibroids, prior to surgery.

Dosage and administration
Adults
One 3.6 mg depot of ‘Zoladex’ injected subcutaneously into the anterior abdominal wall, every 28 days.
Assisted reproduction: ‘Zoladex’ 3.6 mg is administered to downregulate the pituitary gland, as defined by serum oestradiol levels similar to those observed in the early follicular phase (approximately 150 pmol/1). This will usually take between 7 and 21 days.

For use in endometrial thinning; two depots to be administered 4 weeks apart, with surgery timed for between zero and two weeks after the second depot.

For women who are anaemic as a result of uterine fibroids, ‘Zoladex’ 3.6 mg depot with supplementary iron may be given for up to three months before surgery.

Children
‘Zoladex’ is not indicated for use in children.

For correct administration of ‘Zoladex’, see instructions on the instruction card.

Contra-indications
‘Zoladex’ should not be given to patients with a known hypersensitivity to the active substance, to
other LHRH analogues, or to any excipients of this product. ‘Zoladex’ should not be used during pregnancy or lactation.

Warning and precautions
‘Zoladex’ is not indicated for use in children as safety and efficacy have not been established in this group of patients.

Males
The use of ‘Zoladex’ in men at particular risk of developing ureteric obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. If spinal cord compression or renal impairment due to ureteric obstruction are present or develop, specific standard treatment of these complications should be instituted.

Females
The use of LHRH agonists in women may cause a loss of bone mineral density. Currently available ‘Zoladex’ data indicate a mean loss of 4.6% in vertebral bone mineral density following a six month course of treatment with progressive recovery to a mean loss compared to baseline of 2.6% six months after cessation of treatment. In patients receiving ‘Zoladex’ for the treatment of endometriosis, the addition of hormone replacement therapy (a daily oestrogenic agent and a progestogenic agent) has been shown to reduce bone mineral density loss and vasomotor symptoms.

‘Zoladex’ should be used with caution in women with known metabolic bone disease.

‘Zoladex’ may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix.

Currently, there are no clinical data on the effects of treating benign gynaecological conditions with ‘Zoladex’ for periods in excess of six months.

Assisted Reproduction:
‘Zoladex’ 3.6 mg should only be administered as part of a regimen for assisted reproduction under the supervision of a specialist experienced in the area. As with other LHRH agonists, there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of ‘Zoladex’ 3.6 mg, in combination with gonadotrophin. It has been suggested that the downregulation achieved with a depot agonist may lead, in some cases, to an increased requirement for gonadotrophin. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS because its severity and incidence may be dependent on the dose regimen of gonadotrophin. Human chorionic gonadotrophin (hCG) should be withheld, if appropriate.

It is recommended that ‘Zoladex’ 3.6 mg be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome as follicle recruitment may be increased.

Interactions
None known

Pregnancy and lactation
Although reproductive toxicology in animals gave no evidence of teratogenic potential, ‘Zoladex’ should not be used in pregnancy as there is a theoretical risk of abortion or foetal abnormality if LHRH agonists are used during pregnancy. Potentially fertile women should be examined carefully before treatment to exclude pregnancy. Non hormonal methods of contraception should be employed during therapy and in the case of endometriosis until menses are resumed.

Pregnancy should be excluded before ‘Zoladex’ 3.6 mg is used for assisted reproduction. The clinical data from use in this setting are limited but the available evidence suggests there is no causal association between ‘Zoladex’ and any subsequent abnormalities of oocyte development or pregnancy and outcome.

The use of ‘Zoladex’ during breast feeding is not recommended.

Effect on ability to drive or operate machinery
There is no evidence that ‘Zoladex’ results in impairment of these activities.

Undesirable effects
General
Rare incidences of hypersensitivity reactions, which may include some manifestations of anaphylaxis, have been reported.
Arthralgia has been reported. Non-specific paraesthesias have been reported. Skin rashes have been reported which are generally mild, often regressing without discontinuation of therapy.

Changes in blood pressure, manifest as hypotension or hypertension, have been occasionally observed in patients administered ‘Zoladex’. The changes are usually transient, resolving either during continued therapy, or after cessation of therapy with ‘Zoladex’. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of ‘Zoladex’ treatment.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration.

Occasional local reactions include mild bruising at the subcutaneous injection site.

Males
Pharmacological effects in men include hot flushes and sweating and a decrease in potency, seldom requiring withdrawal of therapy. Breast swelling and tenderness have been noted infrequently. Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically. Isolated cases of ureteric obstruction and spinal cord compression have been recorded.

The use of LHRH agonists in men may cause a loss of bone mineral density.

Females
Pharmacological effects in women include hot flushes and sweating, and a change in libido, seldom requiring withdrawal of therapy. Headaches, mood changes including depression, vaginal dryness and change in breast size have been noted infrequently. Initially, breast cancer patients may experience a temporary increase in signs and symptoms, which can be managed symptomatically. In women with fibroids, degeneration of fibroids may occur. Rarely, breast cancer patients with bony metastases have developed hypercalcaemia on initiation of therapy.

In Assisted Reproduction: As with other LHRH agonists, there have been reports of ovarian hyperstimulation syndrome (OHSS), associated with the use of ‘Zoladex’ 3.6 mg in combination with gonadotrophin. It has been suggested that the downregulation achieved with a depot agonist may lead, in some cases, to an increased requirement for gonadotrophin. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS because its severity and incidence may be dependent on the dose regimen of gonadotrophin. Human chorionic gonadotrophin (hCG) should be withheld, if appropriate.

Follicular and luteal ovarian cysts have been reported to occur following LHRH therapy. Most cysts are asymptomatic, non-functional, varying in size and resolve spontaneously.

Overdosage
There is limited experience of overdosage in humans. In cases where ‘Zoladex’ has unintentionally been readministered early, or given at a higher dose, no clinically relevant adverse effects have been seen. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentrations and on the reproductive tract will be evident with higher doses of ‘Zoladex’. If overdosage occurs, this should be managed symptomatically.

Pharmacological Properties
Pharmacodynamic Properties
Mode of action: ‘Zoladex’ (D-Ser(But)6 Azgly10 LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration ‘Zoladex’ results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum oestradiol concentrations in females. This effect is reversible on discontinuation of therapy. Initially, ‘Zoladex’, like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum oestradiol concentration in women. During early treatment with ‘Zoladex’ some women may experience vaginal bleeding of variable duration and intensity. Such bleeding probably represents oestrogen withdrawal bleeding and is expected to stop spontaneously.

In men by around 21 days after the first depot injection testosterone concentrations have fallen to within the castrate range and remain suppressed with continuous treatment every 28 days. This inhibition
leads to prostate tumour regression and symptom-
atic improvement in the majority of patients.
In women serum oestradiol concentrations are sup-
pressed by around 21 days after the first depot
injection and, with continuous treatment every 28
days, remain suppressed at levels comparable with
those observed in postmenopausal women. This
suppression is associated with a response in hor-
mone dependent breast cancer, endometriosis,
uterine fibroids and suppression of follicular de-
velopment within the ovary. It will produce endometrial
thinning and will result in amenorrhoea in the major-
ity of patients.
‘Zoladex’ in combination with iron has been shown to
induce amenorrhoea and improve haemoglobin con-
centrations and related haematological parameters in
women with fibroids who are anaemic. The combina-
tion produced a mean haemoglobin concentration 1 g/
dl above that achieved by iron therapy alone.
During treatment with LHRH analogues patients
may enter the menopause. Rarely, some women do
not resume menses on cessation of therapy.

Pharmacokinetic Properties
The bioavailability of ‘Zoladex’ is almost complete.
Administration of a depot every four weeks ensures
that effective concentrations are maintained with
no tissue accumulation. ‘Zoladex’ is poorly protein
bound and has a serum elimination half-life of two
to four hours in subjects with normal renal function.
The half-life is increased in patients with impaired
renal function. For the compound given monthly in
a depot formulation, this change will have minimal
effect. Hence, no change in dosing is necessary
in these patients. There is no significant change in
pharmacokinetics in patients with hepatic failure.

Preclinical Safety Data
Following long-term repeated dosing with ‘Zoladex’,
an increased incidence of benign pituitary tumours
has been observed in male rats. Whilst this finding
is similar to that previously noted in this species fol-
lowing surgical castration, any relevance to humans
has not been established.
In mice, long term repeated dosing with multiples of
the human dose produced histological changes in
some regions of the digestive system manifested by
pancreatic islet cell hyperplasia and a benign pro-
liferative condition in the pyloric region of the stom-
ach, also reported as a spontaneous lesion in this
species. The clinical relevance of these findings is
unknown.

Precautions for storage
Do not store above 25°C
Instructions for use, handling and disposal
Use as directed by the prescriber. Use only if pouch
is undamaged. Use immediately after opening
pouch.
Dispose of the syringe in an approved sharps col-
llector.

Pack size
Please refer to the outer carton for pack size.

Shelf life
Please refer to expiry date on outer carton.

Date of revision of text
5th January 2006