NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Goserelin, 3.6 mg implant, in a prefilled syringe (Teva)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One implant contains 3.6 mg goserelin (as goserelin acetate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Implant, in a pre-filled syringe

White to off-white cylindrical rods (approximate dimensions: diameter 1.2 mm, length 13 mm, mass 18 mg), embedded in biodegradable polymer matrix.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Goserelin (Teva) 3.6 mg is indicated for the management of:

- Prostate cancer suitable for hormonal manipulation
- Adjuvant and neoadjuvant therapy in combination with radiotherapy for the management of locally advanced prostate cancer in men suitable for hormonal manipulation
- Pre- and peri-menopausal women with hormone receptor positive breast cancer suitable for hormonal manipulation
- Endometriosis: Goserelin (Teva) alleviates symptoms including pain, and reduces the size and number of endometrial lesions.
- Uterine fibroids: Goserelin (Teva) shrinks the lesions, reduces symptoms including pain, and causes cessation of menses in the majority of patients thereby improving haematological status when previous heavy menstrual loss has caused anaemia.
- Endometiral thinning: Use as an endometrial thinning agent prior to endometrial ablation. As a prethinning agent, Goserelin (Teva) 3.6 mg should be administered as two implants, four weeks apart, with surgery planned for between zero and two weeks after the second implant injection.
- Assisted reproduction: Pituitary down regulation in preparation for superovulation.

4.2 Dose and method of administration
Dose

Adults
One 3.6 mg depot of Goserelin (Teva) injected subcutaneously into the anterior abdominal wall, every 28 days.

Use of Goserelin (Teva) in treatment of benign gynaecological conditions should be limited to six months because of possible osteoporotic effects.

Adjuvant and/or neoadjuvant therapy in combination with radiotherapy may include short-term use of an anti-androgen to prevent flare.

For assisted reproduction, once pituitary down regulation has been achieved with Goserelin (Teva), superovulation and oocyte retrieval should be carried out in accordance with normal practice.

Paediatric population
Goserelin (Teva) is not indicated in children.

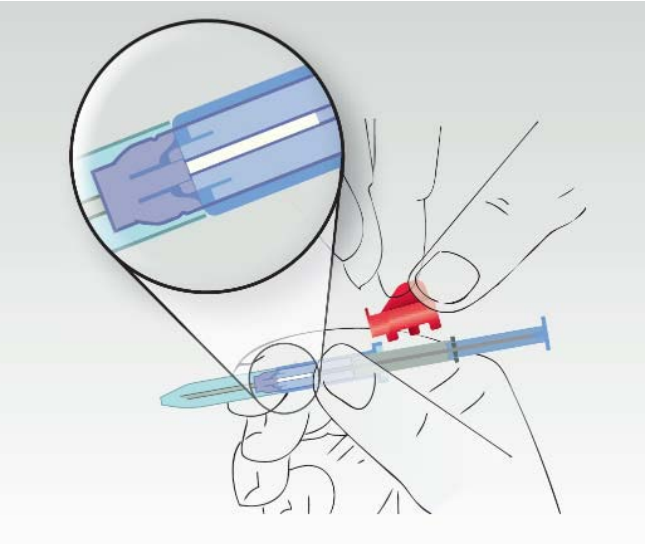
Special populations
No dosage adjustment is necessary for patients with renal or hepatic impairment, or in the elderly.

Method of administration

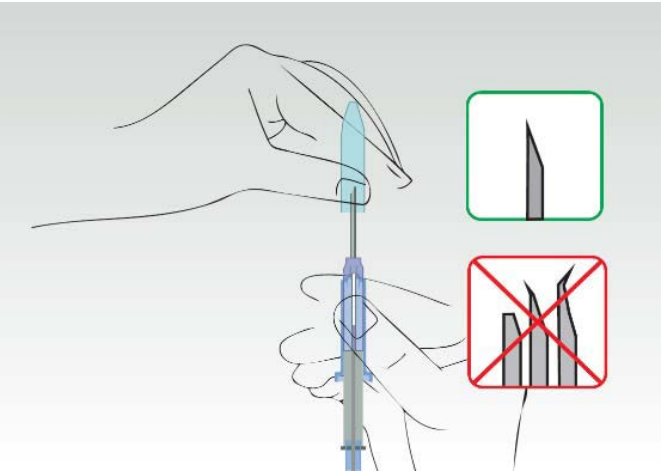
Goserelin (Teva) is indicated for subcutaneous use. For correct administration of Goserelin (Teva), refer to instructions printed on inside of carton.

Use only if pouch is undamaged. Use immediately after opening pouch.

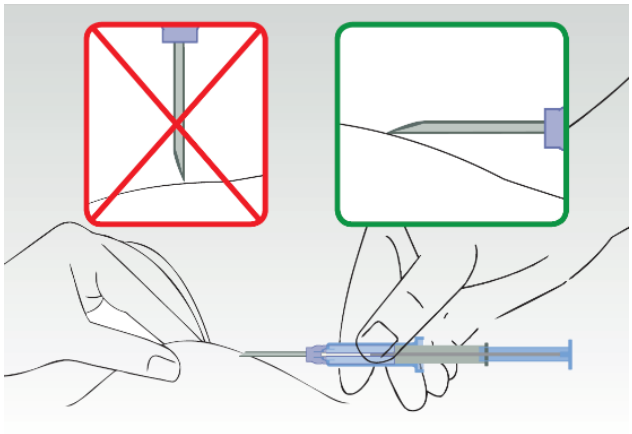
Goserelin (Teva) is administered by subcutaneous injection, according to the following instructions:



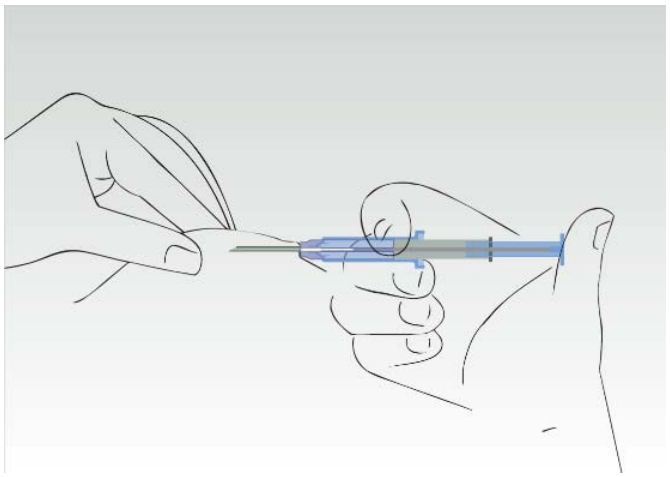
Remove the applicator from the sterile pack.
Check whether the implant is in the intended position in the applicator.
Remove the safety clip.



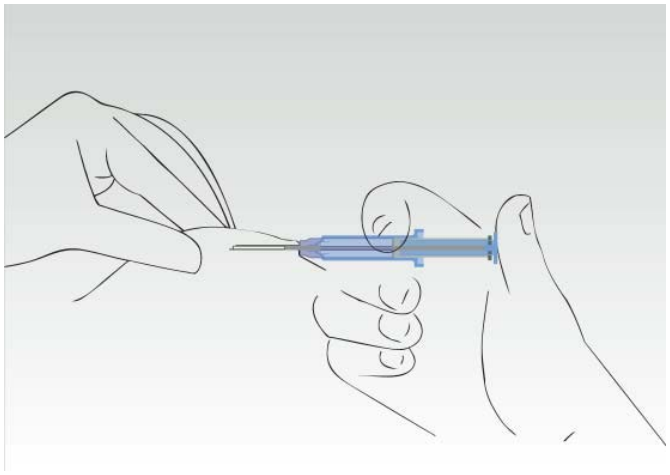
Grip the applicator on the syringe barrel and loosen the protective cap by moving it gently back and forth.
Remove the cap carefully parallel to the needle without contacting the tip of the needle.
After removal of the cap check the integrity of the needle.
Uncareful removal of the cap can damage the tip of the needle.



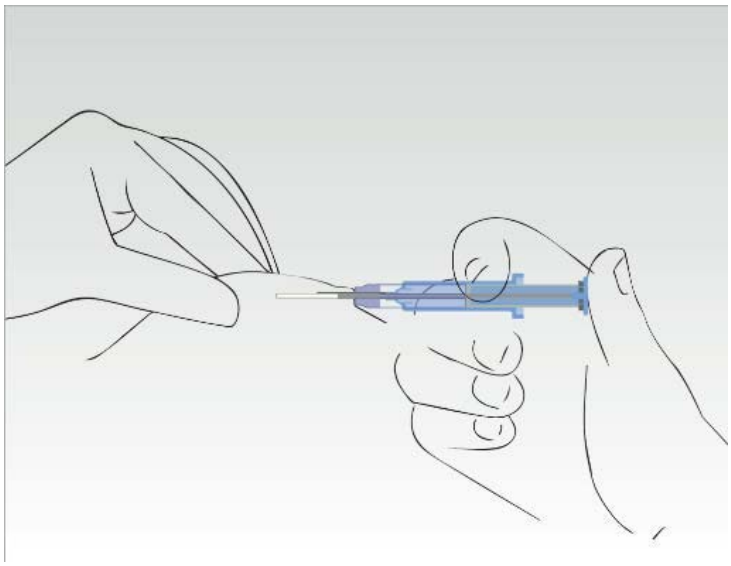
Pinch the patient’s skin together while you are holding the syringe barrel.
Insert the needle **almost parallel to the skin** with the opening of the needle facing up.
Insert the needle into the subcutaneous tissue (not in muscle or into the abdominal cavity) of the anterior abdominal wall under the umbilical line, until the syringe barrel touches the patient's skin.
This contact with the skin must remain during the entire application process.



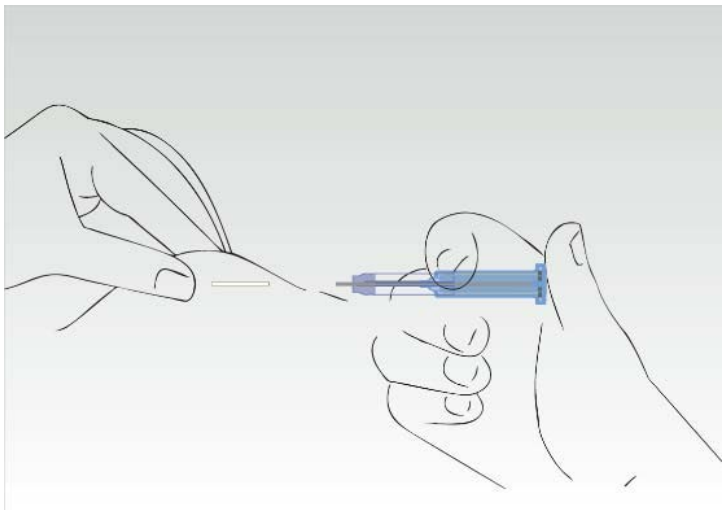
Press the syringe plunger down.
Do not pull the syringe back in any case.
During the application, the syringe barrel has to touch the patient’s skin.



When the plunger is stopped, the needle retraction is unlocked automatically.



The needle is retracted from the tissue into the syringe barrel.
The syringe barrel must remain in contact with the patient's skin.
The plunger movement forward and needle retraction are carried out in one smooth motion.



The application process is completed.
The needle has been fully retracted into the barrel of the syringe.
Visually check the syringe barrel to confirm the implant rod has been delivered to the patient during the application process and completely implanted.
The protuding mandrel protects against injury at the needle tip.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Goserelin (Teva) 3.6 mg is not indicated for use in children, as safety and efficacy have not been established in this group of patients.

Injection site injury has been reported with goserelin administration, including events of pain, haematoma, haemorrhage and vascular injury. Monitor affected patients for signs or symptoms of abdominal haemorrhage. In very rare cases, administration error resulted in vascular injury and haemorrhagic shock requiring blood transfusions and surgical intervention. Extra care should be taken when administering Goserelin (Teva) to patients with a low BMI and/or receiving full anticoagulation medications.

The use of Goserelin (Teva) 3.6 mg 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. Isolated cases have been reported.

Initially Goserelin (Teva), like other LHRH agonists, transiently increases serum testosterone. Some patients may experience a temporary increase in bone pain, which can be managed symptomatically.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus. Consideration should therefore be given to monitoring blood glucose.

An increased risk of developing myocardial infarction and sudden cardiac death has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease.

The use of LHRH agonists may cause a reduction in bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority. Preliminary data suggest the use of goserelin in combination with tamoxifen in patients with breast cancer may reduce bone mineral loss. In patients receiving goserelin 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. In men, preliminary data suggest the use of a bisphosphonate in combination with a LHRH agonist may reduce bone mineral loss.

Following two years treatment for early breast cancer in women, the average loss of BMD was 6.2% and 11.5% at the femoral neck and lumbar spine respectively. This loss has been shown to be partially reversible at the one year off treatment follow-up with recovery to 3.4% and 6.4% relative to baseline at the femoral neck and lumbar spine respectively.

Currently, there are no clinical data on the effects of treating benign gynaecological conditions with Goserelin (Teva) 3.6 mg for periods in excess of six months.

Androgen deprivation therapy may prolong the QT interval, although a causal association has not been established with goserelin. In patients with a history of or who have risk factors for QT prolongation and in patients receiving concomitant medicinal products that may prolong the QT interval (see Interaction with other medicinal products and other forms of interaction) physicians should assess the benefit risk ratio including the potential for Torsade de Pointes prior to initiating Goserelin (Teva).

The use of Goserelin (Teva) may cause an increase in cervical resistance and care should be taken when dilating the cervix.

Assisted Reproduction
Goserelin (Teva) 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 use of Goserelin (Teva) 3.6 mg in combination with gonadotrophins. The stimulation cycle should be monitored carefully to identify patients at risk of developing OHSS. Human chorionic gonadotrophin (hCG) should be withheld if appropriate.

It is recommended that Goserelin (Teva) 3.6 mg be used with caution in assisted reproduction regimens in patients with polycystic ovarian syndrome, as follicle recruitment may be increased.

Paediatric Population
Goserelin (Teva) is not indicated for use in children, as safety and efficacy have not been established in this patient group.

4.5 Interaction with other medicinal products and other forms of interaction
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Goserelin (Teva) with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

4.6 Fertility, pregnancy and lactation
Use in pregnancy
Goserelin (Teva) should not be used during 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 until menses is resumed.

Pregnancy should be excluded before goserelin is used for assisted reproduction. When goserelin is used in this setting, there is no clinical evidence to suggest a causal association between goserelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

Use in lactation
The use of Goserelin (Teva) during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines
There is no evidence that goserelin would result in impairment of ability to drive or operate machinery.

4.8 Undesirable effects
The following frequency categories for adverse drug reactions (ADRs) were calculated based on reports from goserelin clinical trials and post-marketing sources.

The following convention has been used for classification of frequency: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000) and Not known (cannot be estimated from the available data).

Table: Goserelin 3.6 mg adverse drug reactions presented by MedDRA System Organ Class

MedDRA SOC	**Frequency**	**Males**	**Females**
Neoplasms, benign malignant and unspecified (including cysts and polyps)	Very rare	Pituitary tumour	Pituitary tumour
	Not known	N/A	Degeneration of uterine fibroid
Immune system disorders	Uncommon	Drug hypersensitivity	Drug hypersensitivity
	Rare	Anaphylactic reaction	Anaphylactic reaction
Endocrine disorders	Very rare	Pituitary haemorrhage	Pituitary haemorrhage
Metabolism and nutrition disorders	Common	Glucose tolerance impaired[a]	N/A
	Uncommon	N/A	Hypercalcaemia
Psychiatric disorders	Very common	Libido decreased[b]	Libido decreased[b]
	Common	Mood changes, depression	Mood changes, depression
	Very rare	Psychotic disorder	Psychotic disorder
Nervous system disorders	Common	Paraesthesia	Paraesthesia
		Spinal cord compression	N/A
		N/A	Headache
Cardiac disorders	Common	Cardiac failure[f], myocardial infarction[f]	N/A
	Not known	QT prolongation	QT prolongation
Vascular disorders	Very common	Hot flush[b]	Hot flush[b]
	Common	Blood pressure abnormal[c]	Blood pressure abnormal[c]

Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis[b]	Hyperhidrosis[b] , acne[i]
	Common	Rash[d]	Rash[d] , alopecia[g]
	Not known	Alopecia[h]	(see Common)
Musculoskeletal, connective tissue and bone disorders	Common	Bone pain[e]	N/A
		(see Uncommon)	Arthralgia
	Uncommon	Arthralgia	(see Common)
Renal and urinary disorders	Uncommon	Ureteric obstruction	N/A
Reproductive system and breast disorders	Very common	Erectile dysfunction	N/A
		N/A	Vulvovaginal dryness
		N/A	Breast enlargement
	Common	Gynaecomastia	N/A
	Uncommon	Breast tenderness	N/A
	Rare	N/A	Ovarian cyst
		N/A	Ovarian hyperstimulation syndrome (if concomitantly used with gonadotrophins)
	Not known	N/A	Withdrawal bleeding
General disorders and administration site conditions	Very common	(see Common)	Injection site reaction
	Common	Injection site reaction	(see Very common)
		N/A	Tumour flare, tumour pain (on initiation of treatment)
Investigations	Common	Bone density decreased, weight increased	Bone density decreased, weight increased

a A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes mellitus.
b These are pharmacological effects which seldom require withdrawal of therapy.
c These may manifest as hypotension or hypertension, have been occasionally observed in patients administered goserelin. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with goserelin. Rarely, such changes have been sufficient to require medical intervention, including withdrawal of treatment from goserelin.
d These are generally mild, often regressing without discontinuation of therapy.
e Initially, prostate cancer patients may experience a temporary increase in bone pain, which can be managed symptomatically.
f Observed in a pharmaco-epidemiology study of LHRH agonists used in the treatment of prostate cancer. The risk appears to be increased when used in combination with anti-androgens.
g Loss of head hair has been reported in females, including younger patients treated for benign conditions. This is usually mild but occasionally can be severe.
h Particularly loss of body hair, an expected effect of lowered androgen levels.
i In most cases acne was reported within one month after the start of goserelin.

Reduction in glucose tolerance, manifesting as diabetes or loss of glycaemic control in those with pre-existing diabetes, has been reported during treatment with GnRH agonists including Goserelin (Teva) (see Special warnings and precautions for use).

A small increased risk of developing myocardial infarction and sudden cardiac death has been reported in association with use of GnRH agonists in men.

4.9 Overdose

There is limited experience of overdosage in humans. In cases where goserelin has unintentionally been re-administered 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 goserelin. If overdosage occurs, this should be managed symptomatically.

For information on the management of overdose, contact the New Zealand Poison Information Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hormones and related agents, ATC code: L02AE03

Goserelin (D-Ser(But)6 Azgly10 LHRH) is a synthetic analogue of naturally occurring LHRH. On chronic administration goserelin results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum estradiol concentrations in females. This effect is reversible on discontinuation of therapy. Initially, goserelin, like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum estradiol concentration in women.

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 symptomatic improvement in the majority of patients.

In the management of patients with metastatic prostate cancer, goserelin has been shown in comparative clinical trials to give similar survival outcomes to those obtained with surgical castrations.

In a combined analysis of 2 randomised controlled trials comparing bicalutamide 150 mg monotherapy versus castration (predominantly in the form of goserelin), there was no significant difference in overall survival between bicalutamide-treated patients and castration-treated patients (hazard ratio = 1.05 [CI 0.81 to 1.36]) with locally advanced prostate cancer. However, equivalence of the two treatments could not be concluded statistically.

In comparative trials, goserelin has been shown to improve disease-free survival and overall survival when used as an adjuvant therapy to radiotherapy in patients with high-risk localised (T1-T2 and PSA of at least 10 ng/ml or a Gleason score of at least 7), or locally advanced (T3-T4) prostate cancer. The optimum duration of adjuvant therapy has not been established; a comparative trial has shown that 3 years of adjuvant goserelin gives significant survival improvement compared with radiotherapy alone. Neo-adjuvant goserelin prior to radiotherapy has been shown to improve disease-free survival in patients withhigh risk localised or locally advanced prostate cancer.

After prostatectomy, in patients found to have extra-prostatic tumour spread, adjuvant goserelin may improve disease-free survival periods, but there is no significant survival improvement unless patients have evidence of nodal involvement at time of surgery. Patients with pathologically staged locally advanced disease should have additional risk factors such as PSA of at least 10 ng/ml or a Gleason score of at least 7 before adjuvant goserelin should be considered. There is no evidence of improved clinical outcomes with use of neo-adjuvant goserelin before radical prostatectomy.

In women, serum estradiol concentrations are suppressed 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 hormone-dependent advanced breast cancer, uterine fibroids, endometriosis and suppression of follicular development within the ovary. It will produce endometrial thinning and will result in amenorrhoea in the majority of patients.

During treatment with LHRH analogues patients may enter the menopause. Rarely, some women do not resume menses on cessation of therapy.

Goserelin in combination with iron has been shown to induce amenorrhoea and improve haemoglobin concentrations and related haematological parameters in women with fibroids who are anaemic. The combination produced a mean haemoglobin concentration 1 g/dl above that achieved by iron therapy alone.

5.2 Pharmacokinetic properties

The bioavailability of goserelin is almost complete. Administration of a depot every four weeks ensures that effective concentrations are maintained with no tissue accumulations. Goserelin 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.

5.3 Preclinical safety data

Following long-term repeated dosing with goserelin, 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 following surgical castration, any relevance to man 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 proliferative condition in the pyloric region of the stomach, also reported as a spontaneous lesion in this species. The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly(D,L-lactide-co-glycolide) 50:50

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Prior to first opening: 48 months

After first opening: The product should be used immediately after opening of the pouch.

6.4 Special precautions for storage

Store below 30ºC.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Pack size: 1 implant per pack.

Each pack contains a single dose prefilled syringe consisting of three main parts: the body with the implant holder unit, a mandrin and a needle unit. The implant in a prefilled syringe is packed together with a desiccant capsule in a pouch within a cardboard carton.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Auckland, New Zealand
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

19 July 2018

10. DATE OF REVISION OF THE TEXT

17 March 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Method of administration updated to highlight critical steps during implant administration.