NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Goserelin, 10.8 mg implant, in a prefilled syringe (Teva)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 10.8 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 1.5 mm, length 13 mm, mass 44 mg), embedded in biodegradable polymer matrix.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Goserelin (Teva) 10.8 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.
- 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.

4.2 Dose and method of administration

Dose

Adults - Males

One 10.8 mg depot of Goserelin (Teva) injected subcutaneously into the anterior abdominal wall, every 3 months.

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

Adults - Females

One 10.8 mg depot of Goserelin (Teva) injected subcutaneously into the anterior abdominal wall, every 12 weeks.

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 package insert.

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) 10.8 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, 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) 10.8 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.

Initially Goserelin (Teva) 10.8 mg, 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. In patients receiving Goserelin (Teva) 3.6 mg 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 loss and vasomotor symptoms. There is no experience of the use of hormone replacement therapy in women receiving Goserelin (Teva) 10.8 mg. In men, preliminary data suggest the use of a bisphosphonate in combination with a LHRH agonist may reduce bone mineral loss.

In women, Goserelin (Teva) 10.8 mg is only indicated for use in endometriosis and fibroids. For female patients requiring treatment with goserelin for other conditions, refer to the prescribing information for Goserelin (Teva) 3.6 mg.

Time to return of menses after cessation of therapy with Goserelin (Teva) 10.8 mg may be prolonged in some patients.

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

There are no clinical data on the effects of treating benign gynaecological conditions with Goserelin (Teva) 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 (Teva). 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).

Paediatric Population

Goserelin 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) 10.8 mg 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 until menses is resumed (see Special warnings and precautions for use).

Use in lactation

The use of Goserelin (Teva) 10.8 mg during breast feeding 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.

Post-marketing experience
A small number of cases of changes in blood count, hepatic dysfunction, pulmonary embolism and interstitial pneumonia have been reported in connection with goserelin.

4.9 Overdose
There is not much experience of overdose in humans. In cases where goserelin has been given before the planned time of administration, or when a bigger dose of goserelin than originally planned has been given, no clinically significant undesirable effects have been observed. 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. In case of overdose, the condition 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. Initially, goserelin, like other LHRH agonists, may transiently increase serum testosterone concentrations.

In men, by around 21 days after the first depot injection, testosterone concentrations have fallen to within the castrate range and remain suppressed with treatment every 12 weeks.

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.

5.2 Pharmacokinetic properties
Administration of goserelin every 12 weeks ensures that exposure to goserelin is maintained with no clinically significant accumulation. 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 in a 10.8 mg depot formulation every 12 weeks this change will not lead to any accumulation. 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), Poly(D,L-lactide-co-glycolide) 75:25

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 30°C.

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
19 July 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	New data sheet