NEW ZEALAND DATA SHEET
LEUPRORELIN SANDOZ IMPLANT (LEUPRORELIN ACETATE)

1. PRODUCT NAME

LEUPRORELIN SANDOZ, 3.6 mg or 5 mg, implant in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains 3.6 mg or 5 mg leuprorelin (as leuprorelin acetate).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Implant in pre-filled syringe.

Biodegradable white to slightly yellowish cylinder shaped stick (length 10 mm) in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Palliative treatment of patients with advanced hormone-dependent prostate carcinoma.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

The indication for treatment should be established and the long-term therapy monitoring carried out by physicians experienced in tumour therapy.

LEUPRORELIN SANDOZ 3.6 mg:

The recommended dose is a single dose of 3.6 mg once monthly.

After the second administration, its use can be postponed by up to 2 weeks in exceptional cases, without usually impairing the therapeutic effect in most patients (see Section 5.2 Pharmacokinetic properties).

LEUPRORELIN SANDOZ 5 mg:

The recommended dose is a single-dose of 5 mg once every 3 months.

If, in exceptional cases, the date of administration is postponed by up to 4 weeks, in the majority of patients the therapeutic effect should not be impaired (see Section 5.2 Pharmacokinetic properties).

Dosage adjustment in

- renal impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment, or in older people.

- Paediatrics

LEUPRORELIN SANDOZ is contraindicated in children and adolescents see Section 4.3 Contraindications.

Method of administration

One implant is injected subcutaneously into the anterior abdominal wall.

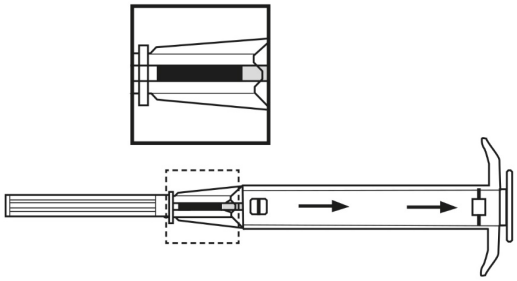
Before injection, a local anaesthetic may be given.

It is recommended that administration of an anti-androgen is started as adjunctive therapy about 5 days before starting LEUPRORELIN SANDOZ (see Section 4.4 Special warnings and precautions for use).

Instructions for use

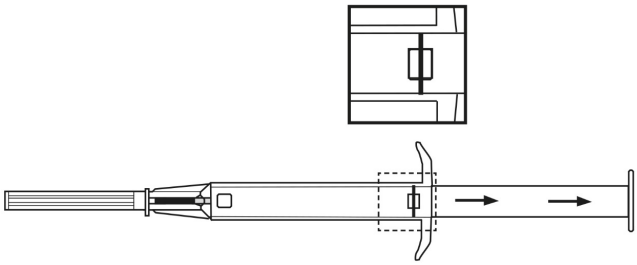
Read these instructions carefully, as the applicator provided with this medicine could be different to others you have used.

1. Disinfect the injection site on the anterior abdominal wall below the navel line.
2. Remove the applicator from the sterile bag and check that the implant is visible in the repository (see framed area). For verifying, view the applicator against a light or gently shake it.



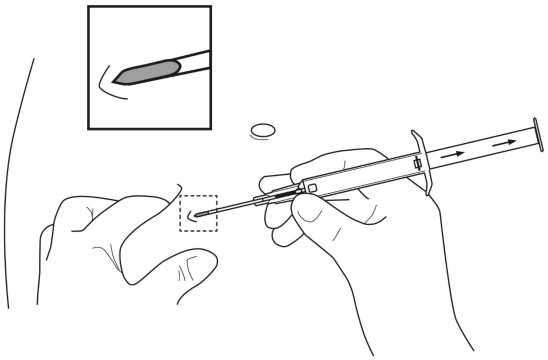
3. Pull the plunger of the applicator **completely backwards until you can see a complete line in the second window.**

   Please note: The plunger can be pushed forward to inject the implant only if it has been previously **pulled back completely!**



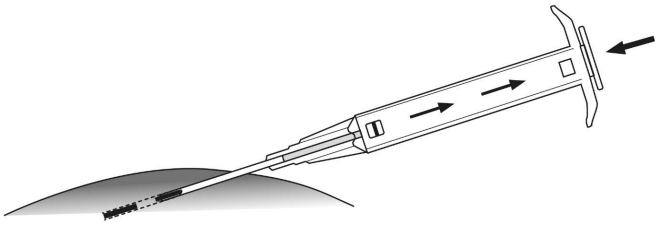
4. Remove the protective cap from the needle.
5. Hold the main body of the applicator with one hand. With the other hand, pinch the patient's skin of the anterior abdominal wall below the navel line. See illustration. With

the **needle opening facing upwards, insert the whole needle**. Do this at a slight angle, almost parallel to the skin into the subcutaneous tissue.

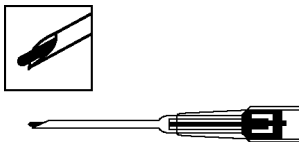


6. Carefully **pull** the applicator approximately **1 cm backwards**. This creates the puncture canal for the implant.

7. Inject the implant into the puncture canal by pushing the plunger **completely** forwards until it snaps into place and you **hear a click**.



8. Withdraw the needle. To ensure that the implant has been injected correctly, check that the light blue tip of the plunger is visible at the tip of the needle.



Both PSA and total testosterone levels in serum must be determined at the beginning and after 3-month use of LEUPRORELIN SANDOZ. The prostatic carcinoma is androgen-sensitive when testosterone concentrations are at castrate level (≤ 0.5 ng/ml) after 3 months and the PSA value has decreased. An early marked decline in the PSA value (approx. 80% of the baseline value) can be seen as a good prognostic indicator for long-term response to androgen withdrawal. Hormone-ablative therapy (e.g. LEUPRORELIN SANDOZ) is then indicated.

When PSA values remain unchanged or have increased in patients with suppressed testosterone, the prostatic carcinoma is androgen-insensitive. In such cases, continuation of hormone-ablative therapy is not suitable.

However, if the patient has shown a clinical response (e.g. improvement in pain and dysuria symptoms, reduction in size of prostate), the result must be considered to be a false negative. In these rare cases, administration of LEUPRORELIN SANDOZ should be continued for another 3 months and the PSA value be checked again; moreover, the patient should be very closely monitored with regard to clinical symptoms.

Therapy of advanced, hormone-dependent prostate carcinoma with LEUPRORELIN SANDOZ is generally a long-term therapy.

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients, or to other LHRH analogues.

Confirmed hormone independence of the carcinoma.

LEUPRORELIN SANDOZ is contraindicated in women and paediatric patients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with hypertension should be carefully monitored.

There is an increased risk of incident depression (which may be severe) in patients being treated with GnRH agonists (gonadotropin-releasing hormone agonists), such as LEUPRORELIN SANDOZ. Patients must be informed of this risk and treated as appropriate if symptoms occur.

Allergic and anaphylactic reactions have been observed. They include both local reactions at the site of injection and systemic symptoms.

Post marketing reports of convulsions have been observed in patients on leuprorelin acetate therapy with or without a history of epilepsy, convulsions or predisposing factors.

Following surgical castration, LEUPRORELIN SANDOZ causes no further reduction of testosterone concentration.

On account of the short-term increase in the serum testosterone concentration at the start of treatment, which can temporarily intensify certain symptoms of disease, patients with a risk of neurological complications, spinal metastasis and urinary tract obstruction should be constantly monitored during the first weeks of treatment, as far as possible as in-patients.

The additional administration of a suitable anti-androgen should be considered for the initial phase of treatment, to mitigate the possible sequelae of the initial testosterone surge and the worsening of the clinical symptoms.

Therapeutic success should be regularly monitored (but particularly if there is evidence of progression despite appropriate treatment) by means of clinical examinations (digital rectal examination of the prostate, ultrasound, skeletal scintigraphy, computed tomography) and by checking phosphatases and/or the prostate specific antigen (PSA) and serum testosterone concentration.

Decreased bone density has been reported following long-term treatment with a GnRH agonist or after an orchiectomy. In patients at risk this may lead to osteoporosis and increased risk of pathological fractures.

A change in glucose tolerance has been reported in some patients being treated with LHRH analogues. Diabetics must be very closely monitored during treatment with LEUPRORELIN SANDOZ.

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see Section 4.5 Interaction with other medicines and other forms of interaction) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating LEUPRORELIN SANDOZ.

Use in the elderly

No data available.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of LEUPRORELIN SANDOZ 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 (see Section 4.4 Special warnings and precautions for use).

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

LEUPRORELIN SANDOZ is intended only for use in male patients.

Use in pregnancy

In reproductive toxicity studies on rabbits, increased foetal mortality and reduced foetal weight were observed. Effects on foetal mortality are anticipated consequences of the pharmacodynamic effect of this substance.

Use in lactation

No data available.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

This medicinal product may alter reactivity to such an extent, even when used as intended, that the ability to drive and use machines is impaired. This is due to the fatigue occurring in a few patients, particularly at the start of treatment, which may also be caused by the underlying tumour disease.

This applies to an even greater extent in combination with alcohol.

4.8. UNDESIRABLE EFFECTS

Initially there is normally a short-term increase in the serum testosterone concentration, which can temporarily aggravate certain symptoms of disease (bone pain or an increase in bone pain, obstruction of the urinary tract and its consequences, spinal cord compression, muscle weakness in the legs, lymphatic oedema). This increase in symptoms normally regresses spontaneously without LEUPRORELIN SANDOZ having to be discontinued.

Undesirable effects may occur due to the withdrawal of the sex hormones.

Tabulated list of adverse reactions:

The side effects are listed based on system organ class and MedDRA frequency convention:

Very common: ≥ 1/10
Common: ≥ 1/100, < 1/10
Uncommon: ≥ 1/1,000, < 1/100
Rare: ≥ 1/10,000, < 1/1,000
Very rare: < 1/10,000
Not known: frequency cannot be estimated from the available data

Leuprorelin Sandoz 3.6 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders					General allergic reactions (fever, skin rash, pruritus, eosinophilia) anaphylactic reactions	
Metabolism and nutrition disorders		Increase in appetite	Decreased appetite, changes in diabetes (increase or decrease in blood glucose levels)			
Psychiatric disorders		Sleep disturbances, mood changes, depression				
Nervous system disorders		Paraesthesia	headache, dizziness		Transient dysgeusia, apoplexy of the pituitary gland*	Convulsions

Leuprorelin Sandoz 3.6 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Cardiac disorders						QT prolongation (see Sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicines and other forms of interaction)
Vascular disorders	hot flushes with outbreaks of sweating		changes in blood pressure (hypertension or hypotension)	thrombosis		
Respiratory, thoracic and mediastinal disorders			Breathing difficulty	Pulmonary embolism		Interstitial lung disease
Gastrointestinal disorders			Diarrhoea		nausea/vomiting	
Skin and subcutaneous tissue disorders			Alopecia, dry skin and mucosa, nocturnal sweating			
Musculoskeletal and connective tissue disorders	Bone pain				Joint and/or back pain and muscle discomfort	Bone demineralisation (see section 4.4 Special warnings and precautions for use)
Renal and urinary disorders		Nocturia, dysuria, pollakiuria	Urinary retention			
Reproductive system and breast disorders	Reduced libido and sexual potency		Testicular size reduction, testicle pain, gynaecomastia			

Leuprorelin Sandoz 3.6 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
General disorders and administration site conditions	Increased diaphoresis				Oedema, tiredness; local skin reactions, e.g. reddening or induration at the site of injection, which usually regresses even when treatment is continued.	In isolated cases, an abscess has appeared at the injection site.
Investigations			Weight gain, weight loss, increase in enzymes such as lactate dehydrogenase (LDH), alkaline phosphatase (AP) or transaminases such as ALT (SGPT), AST (SGOT) or γ-GT.			

Leuprorelin Sandoz 5 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders			General allergic reactions (fever, itching, eosinophilia, skin rash)	Anaphylactic reactions		
Metabolism and nutrition disorders		Decreased appetite, increase in appetite		Changes in diabetic metabolic status (increase or decrease in blood glucose values)		
Psychiatric disorders		Mood changes, depression, sleep disorders				

Leuprorelin Sandoz 5 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Nervous system disorders		Headache, paraesthesia		Vertigo, transient dysgeusia	Apoplexy of the pituitary gland after initial administration of leuprorelin in patients with pituitary adenoma*	Convulsions
Cardiac disorders						QT prolongation (see Sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicines and other forms of interaction)
Vascular disorders	Hot flushes			Changes in blood pressure (hypertension or hypotension), thrombosis		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism		Interstitial lung disease
Gastrointestinal disorders		Nausea/vomiting	Diarrhoea			
Skin and subcutaneous tissue disorders			Dry skin or mucosa, nocturnal sweating	Alopecia		
Musculoskeletal and connective tissue disorders	Bone pain	Joint and/or back pain, myasthenia				Bone demineralisation (see section 4.4 Special warnings and precautions for use)
Renal and urinary disorders		Nocturia, dysuria, pollakiuria	Urinary retention			

Leuprorelin Sandoz 5 mg						
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Reproductive system and breast disorders	Reduction in - or loss of - libido and sexual potency, reduction in size of the testicles	Gynaecomastia	Testicular pain			
General disorders and administration site conditions	Increased sweating, reactions at the injection site e.g. reddening, pain, oedema, itching which usually subsided even when treatment was continued.	Fatigue, peripheral oedema				
Investigations	Weight gain	Weight loss, increases in LDH, transaminases (ALT, AST), gamma-GT and alkaline phosphatase, which may also be a manifestation of the underlying disease.				

**Pituitary apoplexy:* As with other medicinal products in this substance class, there have been reports of very rare cases of pituitary apoplexy following initial administration of leuprorelin in patients with pituitary adenoma.

There have been post-marketing reports of interstitial pneumonia mainly in Japan.

There has been an isolated case of thrombosis of the central retinal artery.

Special notes

The response to LEUPRORELIN SANDOZ therapy can be monitored by measuring serum concentrations of testosterone, acid phosphatase and PSA (prostate-specific antigen).

Testosterone levels initially increase upon initiation of therapy, but decreases over a period of 2 weeks. After 2 - 4 weeks, the testosterone concentrations reached are comparable to those observed following bilateral orchiectomy, remaining then constant over the entire treatment period.

A transient increase in acid phosphatase levels may occur in the initial phase of treatment. Normal levels or levels approaching normal are usually reached again after a few weeks.

In rare cases injection abscesses have occurred. In one case of injection abscesses inadequate absorption of leuprorelin from the depot formulation was observed, therefore testosterone levels should be monitored in such cases. ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9. OVERDOSE

No symptoms of intoxication have been observed to date.

Even when doses were administered of up to 20 mg leuprorelin acetate per day for 2 years, as was the case in the first clinical studies, no other or new undesirable effects were observed which differed from those occurring after daily administration of 1 mg or three-monthly administration of 11.25 mg.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Endocrine therapy, Hormones and related agents, Gonadotropin releasing hormone analogues ATC code: L02AE02

Mechanism of action

Leuprorelin acetate, the active substance of LEUPRORELIN SANDOZ, is a synthetic analogue of the naturally-occurring hypothalamic "releasing factor" LHRH, which controls the release of the gonadotropic hormones LH (luteinising hormone) and FSH (follicle-stimulating hormone) from the anterior lobe of the pituitary gland. These hormones in turn stimulate the synthesis of gonadal steroids.

Unlike physiological LHRH, which is released in a pulsatile manner from the hypothalamus, leuprorelin acetate - also known as LHRH agonist - blocks the LHRH receptors of the pituitary gland continuously during long-term therapy, and after initial short-term stimulation causes their down regulation. As a result, there is reversible pituitary suppression of gonadotropin release with a subsequent decrease in testosterone concentrations.

The testosterone concentration is lowered and this consequently influences growth carcinomatous prostate tissue, which is normally stimulated by dihydrotestosterone, produced by the reduction of testosterone in prostatic cells.

Continuous administration of leuprorelin acetate leads to a decrease in the number and/or sensitivity (so-called "down regulation") of receptors in the pituitary gland, and consequently to a decrease in the concentrations of LH, FSH and DHT. In the process, the testosterone level is reduced to the castration level.

An anti-androgenic effect and growth inhibition of prostatic carcinomas have also been demonstrated in animal trials.

According to preclinical and clinical studies, monthly treatment with leuprorelin acetate inhibits the release of gonadotropin after initial stimulation.

In man, subcutaneous administration of leuprorelin acetate causes an initial increase in LH (luteinising hormone) and FSH (follicle-stimulating hormone), characterised by a transient increase in concentrations of testosterone and dihydrotestosterone.

Since an associated short-term symptomatic aggravation of the disease has been observed in the first 3 weeks in isolated cases, adjuvant administration of anti-androgens is to be considered in men with prostate carcinoma.

In contrast, long-term therapy with leuprorelin acetate causes a decrease in LH and FSH concentrations in all patients; androgen concentrations in men are reached similar to those following bilateral orchiectomy. These changes usually appear 2 - 3 weeks after start of therapy and are maintained for the entire treatment period. For that reason, the hormonal sensitivity of prostatic carcinomas and the possible therapeutic value of orchiectomy can also be investigated with leuprorelin acetate. If necessary, orchiectomy may be replaced by monthly administration of leuprorelin acetate. So far, it has been possible to maintain castrate testosterone levels following continuous administration of leuprorelin acetate over 5 years.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

For 3.6 mg strength:

Following injection of the implant, leuprorelin acetate (the active substance) is continuously released from the polymer (consisting of glycolic acid and lactic acid at a 1:1 ratio) over a period of 1 month. The polymer is absorbed in the same way as surgical suture material.

Within 1 hour, serum levels of 676 pg/ml are measured. Detectable levels of leuprorelin in serum are present for more than 1 month. After two LEUPRORELIN SANDOZ injections, given at an interval of 28 days, detectable serum leuprorelin levels are present for up to 67 days after initial dosing.

For 5 mg strength:

The active substance, leuprorelin acetate, is continuously released from the polylactic acid polymer over a period of up to 182 days (26 weeks) following injection of the LEUPRORELIN SANDOZ biodegradable implant. The polymer is absorbed in the same way as surgical suture material.

Within 2 hours after subcutaneous single-dose application of LEUPRORELIN SANDOZ peak serum leuprorelin levels of 5216 pg/ml (5.2 ng/ml) have been measured.

The AUC during 3 months' treatment with LEUPRORELIN SANDOZ was 32.4 ng/ml*d.

Detectable levels in serum are present for up to 182 days (26 weeks) after administration.

Distribution

The volume of distribution for leuprorelin is 36 l in men.

Excretion

Total clearance is 139.6 ml/min.

Special populations

In patients with impaired renal or hepatic function, leuprorelin levels were in the range of those seen in patients with healthy kidneys or livers. In some patients with chronic renal failure, higher leuprorelin serum levels were measured. However, this observation does not seem to be of any clinical relevance.

5.3. PRECLINICAL SAFETY DATA

Preclinical studies on LEUPRORELIN SANDOZ have shown effects on the reproductive organs, which were expected on the basis of known pharmacological properties of leuprorelin.

Genotoxicity

In vitro and *in vivo* studies on leuprorelin acetate for the detection of genetic and chromosome mutations yielded no evidence of any mutagenic potential.

Carcinogenicity

In rats, a dose-dependent increase in pituitary adenomas was observed following subcutaneous injection of doses of 0.6 - 4 mg/kg/day over 12 and 24 months. No such effect was observed in mice over 24 months.

Local tolerance

Non-clinical studies on dogs and rabbits revealed a good local tolerance of LEUPRORELIN SANDOZ.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

3.6 mg strength: Poly(lactic-co-glycolic acid) 1:1

5 mg strength: Polylactic acid

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

3.6 mg strength: 3 years

4 mg strength: 4 years.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5. NATURE AND CONTENTS OF CONTAINER

Pre-filled plastic syringe of polycarbonate with a plunger of acrylonitrile-butadiene-styrene copolymer and a needle sealed in a bag of polyethylene terephthalate/aluminium PE composite foil. The bag also contains a sodium aluminium silicate desiccant.

Pack sizes:

1 x 1 implant with 3.6 mg or 5 mg leuprorelin (as leuprorelin acetate)

2 x 1 implant with 3.6 mg or 5 mg leuprorelin (as leuprorelin acetate)

3 x 1 implant with 3.6 mg or 5 mg leuprorelin (as leuprorelin acetate)

5 x 1 implant with 3.6 mg or 5 mg leuprorelin (as leuprorelin acetate)

Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149
Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

10 November 2016

10. DATE OF REVISION OF THE TEXT

30 October 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat
4.4	Addition of precautionary statements
4.8	Addition of adverse events