## 1. NAME OF THE MEDICINAL PRODUCT

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG
LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG
Each implant contains 3.6 mg leuprorelin.

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG
Each implant contains 5 mg leuprorelin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG***
Implant in syringe (diameter 1.55 mm, length 10.3 mm). White to slightly yellow rod with a homogenous surface, one rod is packed into a syringe with a desiccant in an aluminium bag.

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG***
Implant in syringe (diameter 1.55 mm, length 10 mm). White to slightly yellowish implant with a uniform surface, one implant in each syringe (packed in an aluminium bag).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

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

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG***
The recommended dose is a single dose of 3.6 mg leuprorelin once monthly.

After the second administration, if, in exceptional cases, the date of administration is postponed by up to 2 weeks, the therapeutic effect is not expected to be impaired in the majority of patients (see section 5.2).

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG***
The recommended dose is a single-dose of 5 mg leuprorelin once every 3 months.

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

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

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE is contraindicated in children and adolescents (see section 4.3).

Monitoring advice
Response to treatment with LEUPRORELIN SANDOZ IMPLANT IN SYRINGE should be monitored by measuring serum concentrations of prostate-specific antigen and testosterone periodically.

Therapy of advanced prostate carcinoma with LEUPRORELIN SANDOZ IMPLANT IN SYRINGE is generally a long-term therapy.

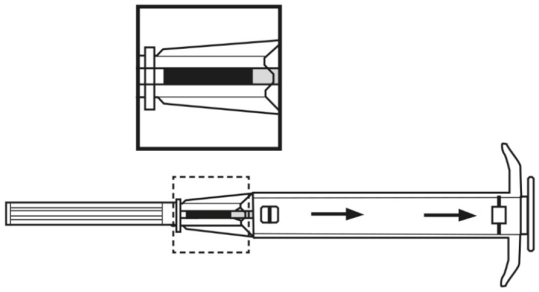
Method of administration
One implant is injected subcutaneously into the anterior abdominal wall, where it forms a drug delivery depot to hydrolytically degrade, releasing the active substance. It provides continuous release of leuprorelin for one month for LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG and for three months for LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG.

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE is for use in one patient on one occasion only. It contains no antimicrobial preservative.

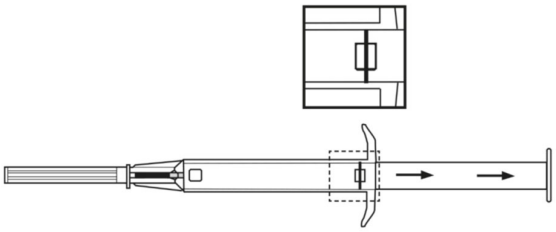
Before injection, a local anaesthetic may be given.

It is recommended that administration of an anti-androgen is started as adjunctive therapy about 5 days before starting LEUPRORELIN SANDOZ IMPLANT IN SYRINGE (see section 4.4).

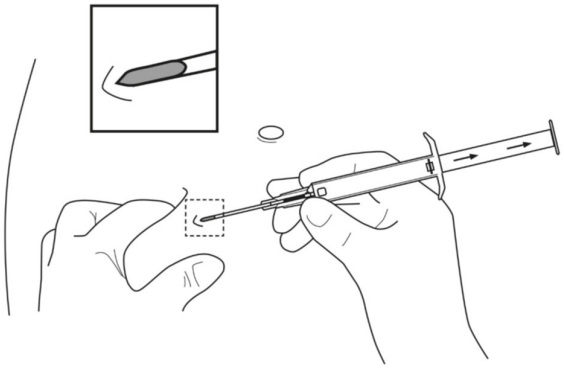
Instructions for use
1. Disinfect the injection site on the anterior abdominal wall below the navel line.
2. Remove the applicator from the sterile bag and check that the implant is visible in the repository (see framed area). For verifying, view the applicator against a light or gently shake it.



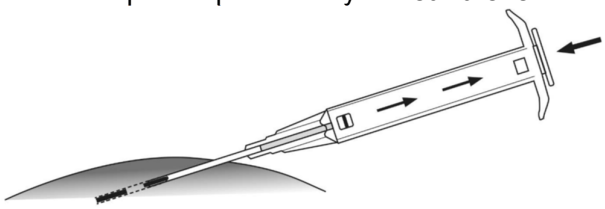
3. Pull the plunger of the applicator **completely backwards until you can see a complete line in the second window**.
   **Please note:** The plunger can only be pushed forward to inject the implant if it has been previously **pulled back completely!**



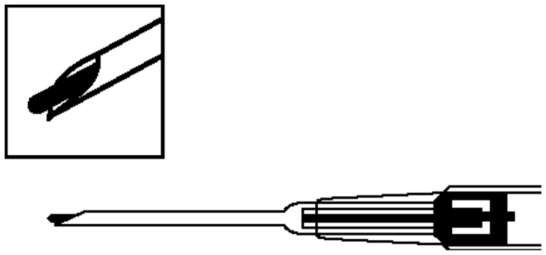
4. Remove the protective cap from the needle.
5. Hold the main body of the applicator with one hand. With the other hand pinch the patient's skin of the anterior abdominal wall below the navel line. See illustration. With the needle **opening facing upwards, insert the whole needle**. Do this at a slight 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 tip (light blue tip for 5mg implant/ white tip for 3.6mg implant) of the plunger is visible at the tip of the needle.



## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients, or to other GnRH analogues.

Confirmed hormone independence of the carcinoma.

Leuprorelin 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 depression (which may be severe) in patients being treated with GnRH agonists (gonadotropin-releasing hormone agonists) such as leuprorelin. Patients must be informed of this risk and be 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 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.

Hypogonadism occurring with long-term treatment with LHRH analogues and/or orchiectomy can lead to osteoporosis with an increased risk of fracture, the development of osteoporosis being more marked following orchiectomy, with increased cortisol levels, than following administration of LHRH analogues. In high-risk patients the additional administration of a bisphosphonate may prevent bone demineralisation.

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 IMPLANT IN SYRINGE.

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) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating LEUPRORELIN SANDOZ IMPLANT IN SYRINGE.

*Idiopathic intracranial hypertension*
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving leuprorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of leuprorelin should be considered.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 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).

## 4.6 Pregnancy and lactation

LEUPRORELIN SANDOZ IMPLANT IN SYRINGE is intended only for use in male patients.

## 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 when combined 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 having to be discontinued.

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

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG***

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

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
Not known: frequency cannot be estimated from the available data

**Immune system disorders**

*Very rare:* General allergic reactions (fever, skin rash, pruritus, eosinophilia), anaphylactic reactions

**Metabolism and nutrition disorders**

*Common:* Increased appetite
*Uncommon:* Decreased appetite, changes in diabetes (increase or decrease in blood glucose levels), weight gain, weight loss

**Psychiatric disorders**

*Common:* Sleep disturbances, mood changes, depression

**Nervous system disorders**

*Common:* Paraesthesia
*Uncommon:* Headache, dizziness
*Very rare:* Transient dysgeusia
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.
*Not known*: Convulsions, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)

**Cardiac disorders**

*Not known*: QT prolongation (see sections 4.4 and 4.5)

**Vascular disorders**

*Very common*: Hot flushes with outbreaks of sweating

*Uncommon:* Changes in blood pressure (hypertension or hypotension)
*Rare:* Thrombosis

**Respiratory, thoracic and mediastinal disorders**
*Uncommon:* Breathing difficulty
*Rare:* Pulmonary embolism
*Not known:* Interstitial lung disease

**Gastrointestinal disorders**
*Uncommon:* Diarrhoea
*Very rare:* Nausea/vomiting

**Skin and subcutaneous tissue disorders**
*Uncommon:* Alopecia, dry skin and mucosa, nocturnal sweating

**Musculoskeletal and connective tissue disorders**
*Very common:* Bone pain
*Very rare:* Joint and/or back pain and muscle discomfort
*Not known:* Bone demineralisation

**Renal and urinary disorder**
*Common*: Nycturia, dysuria, pollakiuria
*Uncommon*: Urinary retention

**Reproductive system and breast disorders**
*Very common:* Reduced libido and sexual potency
*Uncommon:* Testicular size reduction, testicle pain, gynaecomastia

**General disorders and administration site conditions**
*Very common:* Increased sweating
*Very rare:* Oedema, tiredness; local skin reactions, e.g. reddening or induration at the site of injection, which usually regresses even when treatment is continued.
*Not known*: In isolated cases an abscess has appeared at the injection site

**Investigations**
*Uncommon:* Increase in enzymes such as lactate dehydrogenase (LDH), alkaline phosphatase (AP) or transaminases such as ALT (SGPT), AST (SGOT) or γ-GT.

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 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 then decrease 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.

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG***

The side effects are listed based on system organ class and MedDRA frequency convention:
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
Not known: frequency cannot be estimated from the available data

**Immune system disorders**
*Uncommon:* General allergic reactions (fever, itching, eosinophilia, skin rash)
*Rare*: Anaphylactic reactions

**Metabolism and nutrition disorders**
*Very common:* Weight gain
*Common:* Decreased appetite, increased appetite, weight loss
*Rare:* Changes in diabetic metabolic status (increase or decrease in blood glucose values)

**Psychiatric disorders**
*Common:* Depression, sleep disorders, mood changes

**Nervous system disorders**
*Common:* Headache, paraesthesia
*Rare:* Vertigo, transient dysgeusia
*Very rare:* 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
*Not known*: Convulsions, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)

**Cardiac disorders**
*Not known*: QT prolongation (see sections 4.4 and 4.5)

**Vascular disorders**
*Very common:* Hot flushes
*Rare:* Changes in blood pressure (hypertension or hypotension), thrombosis

**Respiratory, thoracic and mediastinal disorders**
*Rare:* Pulmonary embolism
*Not known:* Interstitial lung disease

**Gastrointestinal disorders**
*Common:* Nausea/vomiting
*Uncommon:* Diarrhoea

**Skin and subcutaneous tissue disorders**
*Uncommon:* Dry skin or mucosa, nocturnal sweating
*Rare:* Alopecia

**Musculoskeletal and connective tissue disorders**
*Very common:* Bone pain
*Common:* Joint and/or back pain, myasthenia
*Not known:* Bone demineralisation (see section 4.4)

**Renal and urinary disorders**
*Common:* Nocturia, dysuria, pollakiuria
*Uncommon*: Urinary retention

**Reproductive system and breast disorders**
*Very common:* Reduction in - or loss of - libido and sexual potency, reduction in size of the testicles
*Common:* Gynaecomastia
*Uncommon:* Testicular pain

**General disorders and administration site conditions**
*Very common:* Increased sweating; reactions at the injection site, e.g. reddening, pain, oedema, itching which usually subsided even when treatment was continued.
*Common:* Fatigue, peripheral oedema

**Investigations**
*Common:* Increases in LDH, transaminases (ALT, AST), γ-GT and alkaline phosphatase, which may also be a manifestation of the underlying disease.

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

Special notes
The response to leuprorelin 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.

### 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 monthly administration of 3.75 mg *[Leuprorelin Implant 3.6 mg]* / three-monthly administration of 11.25 mg *[Leuprorelin Implant 5 mg]*.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Mechanism of action**
Pharmacotherapeutic group: Hormones and related agents, Gonadotropin releasing hormone analogues.
ATC code: L02AE02

Leuprorelin acetate, the active substance of LEUPRORELIN SANDOZ IMPLANT IN SYRINGE, 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 (DHT), 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 nonclinical 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 and FSH, 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**

***3.6 mg implant***

Study 2002-18-IMP-3 (HEX2)

The efficacy, safety, pharmacokinetics (PK) and pharmacodynamics of leuprorelin 3.6 mg were investigated in an open-label, multicentre, controlled phase III study (IMP-3) of 4 single injections of leuprorelin 3.6 mg implant (n=30) or comparator treatment leuprorelin 3.57 mg in lyophilised microspheres (n=33), in patients with advanced prostatic cancer. There was an interval of 28 days between injections.

The primary endpoints were 1) the proportion of subjects with successful testosterone suppression; defined as testosterone levels of ≤ 0.5 ng/mL for at least 2 consecutive samples within 8 weeks after the first administration and continuing thereafter up to 8 weeks after the first administration, except for escapes and 2) the proportion of subjects with a testosterone level ≤ 0.5 ng/mL at week 16 after having been successfully suppressed within the first 8 weeks after administration and remaining below ≤ 0.5 ng/mL up to week 16, except for escapes. Secondary endpoints comprised 19 efficacy, endocrine, PK and safety parameters.

In this study, most patients in the Intention-to-Treat (ITT) population experienced successful testosterone suppression within 8 weeks (90% implant, 82% lyophilised microspheres) and remained below the castration level until week 16 (80% implant, 76% lyophilised microspheres). There were no relevant differences in testosterone levels between groups at weeks 4, 8, 12 and 16. The median time to onset of castration level was approximately 4 weeks in both groups and the duration of testosterone suppression was similar.

The changes in concentrations of prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) were similar for both groups as well as the rate of patients with normal PSA values at each visit. Differences in other secondary efficacy endpoints between the groups were not relevant.

Study 2002-19-IMP-4 (HEX3)

In an uncontrolled study with identical design, procedures and endpoints as IMP-3 (except for lack of control and PK blood sampling times), leuprorelin 3.6 mg was investigated in 20 patients with advanced prostatic cancer. In this study (IMP-4), all patients experienced successful testosterone suppression within 8 weeks and remained below the castration level until week 16 (ITT population).

***5 mg implant***

Single dose studies 2001-33-IMP-8 and 2001-34-IMP-9

The efficacy, safety, pharmacokinetics and pharmacodynamics of a single dose of leuprorelin 5 mg were investigated in two open-label, multicentre studies of patients with histologically confirmed advanced adenocarcinoma of the prostate. One study (IMP-8) included randomisation to leuprorelin 5 mg implant (n=33) or comparator treatment leuprorelin 10.72 mg in lyophilised microspheres (n=28) and in the other, uncontrolled, study, patients received leuprorelin 5 mg implant (n=33).

The primary endpoint was the proportion of patients with successful testosterone suppression at week 8 and with a testosterone level ≤ 0.5 ng/mL at week 12. Secondary endpoints included other efficacy, endocrine, PK and safety parameters.

In study IMP-8, most patients in the ITT population experienced successful testosterone suppression within 8 weeks (94% implant, 79% lyophilised microspheres) and remained below the castration level until week 12 (90% implant, 75% lyophilised microspheres).

In study IMP-9, 97% patients experienced successful testosterone suppression within 8 weeks and 91% remained below the castration level until week 12 following a single dose of leuprorelin 5 mg implant (ITT population).

Multiple dose studies 2003-65-IMP-12 and 2003-66-IMP-13

The efficacy, safety, pharmacokinetics and pharmacodynamics of multiple doses of leuprorelin 5 mg were investigated in two open-label, multicentre studies of patients with histologically confirmed advanced adenocarcinoma of the prostate. In study IMP-12, patients received 2 injections of leuprorelin 5 mg separated by 12 weeks (n=18) and in study IMP-13, the 2 injections were separated by 16 weeks (n=16).

The primary endpoint was the proportion of patients with successful testosterone suppression at week 8 (except for escapes) and with a testosterone level ≤ 0.5 ng/mL at week 24 for IMP-12 or week 32 for IMP-13 (except for escapes). Secondary endpoints included other efficacy, endocrine, PK and safety parameters.

In study IMP-12, testosterone suppression was confirmed in 94% patients at week 8, 83% at week 12 and 78% at week 24 (ITT population). There were no relevant differences in testosterone levels between the two treatment intervals (2 injections of leuprorelin 5 mg separated by 12 weeks). Median testosterone levels remained stable throughout the study following the two subcutaneous injections.

In study IMP-13, testosterone suppression was confirmed in 100% patients at week 8, 94% at week 16 and 94% at week 32 (ITT population). There were no relevant differences in testosterone levels between the two treatment intervals (2 injections of leuprorelin 5 mg separated by 16 weeks). Median testosterone levels remained stable throughout the study following the two subcutaneous injections.

## 5.2 Pharmacokinetic properties

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

Absorption
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 3.6 mg injections, given at an interval of 28 days, detectable serum leuprorelin levels are present for up to 67 days after initial dosing.

Distribution
The volume of distribution for leuprorelin is 36 L in men; total clearance is 139.6 mL/min.

Patients with impaired renal or hepatic function
In patients with impaired renal function, higher leuprorelin levels were measured in some cases. Conversely, levels were lower in patients with impaired hepatic function. This observation, however, does not seem to be of any clinical relevance.

**5 mg implant**
The active substance, leuprorelin acetate, is continuously released from the lactic acid polymer over a period of up to 182 days (26 weeks) following injection of the leuprorelin 5 mg biodegradable implant. The polymer is absorbed in the same way as surgical suture material.

Absorption
Within 2 hours after subcutaneous single-dose application of leuprorelin 5 mg, peak serum leuprorelin levels of 5216 pg/mL (5.2 ng/mL) have been measured.

The AUC during 3 months' treatment with leuprorelin 5 mg 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; total clearance is 139.6 mL/min.

Patients with impaired renal or hepatic function
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

**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**
Two year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related incidence of pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). This study also revealed an increased incidence of pancreatic islet cell adenomas, but their incidence showed a negative trend with dose, suggesting that it may not be drug-related. In mice, no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. In short term toxicity studies in mice treated for 3 months with 20-200 mg/kg, hypertrophic and castration cells were found in the anterior pituitary. Neither pituitary nor pancreatic changes were found in cynomolgus monkeys treated for 12 months with 10 mg/kg daily.

**Local tolerance**
Non-clinical studies in dogs and rabbits revealed a good local tolerance of leuprorelin.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG***
Poly(lactic-co-glycolic acid) 1:1

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG***
Polylactic acid

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

Please refer to outer carton.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 3.6 MG***
Pre-filled plastic syringe of polycarbonate with a plunger of acrylonitril-butadien-styrene copolymer and a needle sealed in a bag of polyethylene terephthalate/aluminium/PE composite foil. The bag also contains a desiccant.

Pack sizes:
1 x 1 implant with 3.6 mg leuprorelin (as acetate)
2 x 1 implant with 3.6 mg leuprorelin (as acetate)
3 x 1 implant with 3.6 mg leuprorelin (as acetate)
5 x 1 implant with 3.6 mg leuprorelin (as acetate)
10 x 1 implant with 3.6 mg leuprorelin (as acetate)

Not all pack sizes may be marketed.

***LEUPRORELIN SANDOZ IMPLANT IN SYRINGE 5 MG***
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.

Pack sizes:
1 x 1 implant with 5 mg leuprorelin (as acetate)
2 x 1 implant with 5 mg leuprorelin (as acetate)
3 x 1 implant with 5 mg leuprorelin (as acetate)
5 x 1 implant with 5 mg leuprorelin (as acetate)
10 x 1 implant with 5 mg leuprorelin (as acetate)

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

## 7. MANUFACTURER

EVER Pharma Jena GmbH
Otto-Schott-Strasse 15
07745 Jena
Germany

## 8. DATE OF REVISION OF THE TEXT

FEB 2023
CDS v06_11_2022