PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

LEUPROLIDE HEXAL 5 (implant)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LEUPROLIDE HEXAL 5 implant contains 5,25 mg leuprorelin acetate equivalent to 5 mg leuprorelin.

3. PHARMACEUTICAL FORM

Implant.

White to slightly yellowish implant with a uniform surface, one implant in each syringe, sealed in a sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with advanced hormone-dependent prostate carcinoma.

4.2 Posology and method of administration

Posology:

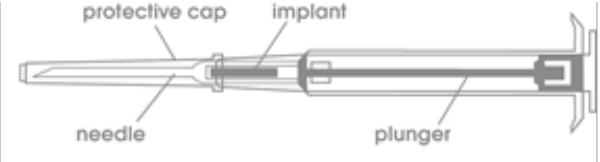
The recommended dose is a single dose of LEUPROLIDE HEXAL 5 once every 12 weeks.

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

Method of administration:

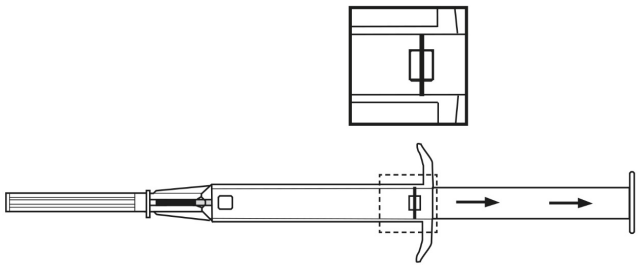
Application should be performed by a medical practitioner experienced in tumour therapy. The implant is inserted subcutaneously into the abdominal skin.

Directions for use:

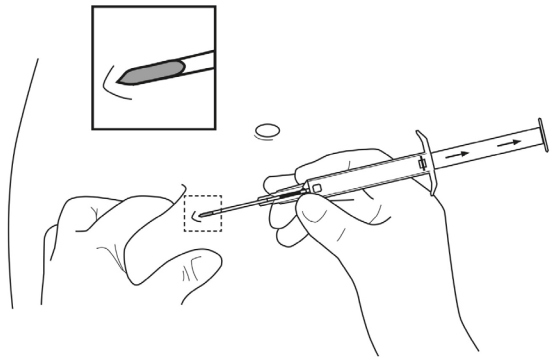


1. Disinfect the injection site on the anterior abdominal wall below the navel line.
2. Remove the syringe from the sterile bag and check that the implant is visible in the repository (see framed area). For verifying, view the syringe against a light or gently shake it.
3. Pull the plunger of the syringe **completely backwards until you can see a complete line in the second window.**

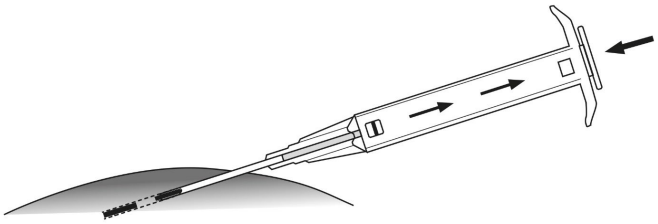
   Note: The plunger can only be pushed forward to inject the implant if it has been previously pulled **back completely.**

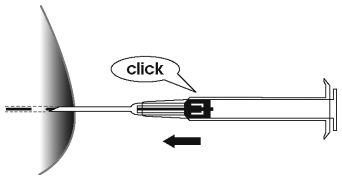


4. Remove the protective cap from the needle.
5. Hold the main body of the syringe with one hand. With the other hand, pinch the patient's skin of the anterior abdominal wall below the navel line. See illustration. With the **needle opening facing upwards, insert the whole needle.** Do this at a slight angle, almost parallel to the skin into the subcutaneous tissue.

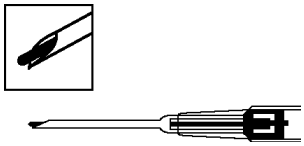


6. Carefully pull the syringe approximately 1 cm backwards. This creates the puncture canal for the implant.





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



8. Ensure safe disposal of the device and needle.

The androgen-sensitivity of advanced prostatic carcinomas must be assessed at 3 months. The main diagnostic parameter is the serum PSA concentration (prostate-specific antigen), which is usually above 10 ng/mℓ at the advanced tumour stage. In the test, the behaviour of PSA values is investigated after androgen withdrawal is induced by LEUPROLIDE HEXAL 5.

Both PSA and total testosterone levels in serum must therefore be determined at the beginning and after 3-month use of LEUPROLIDE HEXAL 5.

The test result is positive 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. LEUPROLIDE HEXAL 5) is then indicated.

The test result is negative when PSA values remain unchanged or have increased in patients with suppressed testosterone. 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 symptomatology and dysuric complaints, reduction in prostatic size), a false-negative result must be taken into consideration. In these rare cases, administration of LEUPROLIDE HEXAL 5 should be continued over a further 3 months and the PSA value be reviewed; in addition, the patient should be closely monitored with regards to clinical symptomatology.

Therapy of advanced, hormone-dependant prostatic carcinomas with LEUPROLIDE HEXAL 5 usually involves long-term treatment. Therapeutic success should be monitored at regular intervals (especially when there are signs of progression despite adequate therapy) via clinical examinations (rectal palpations of the prostate gland, sonography, bone scanning, computerised tomography) and by monitoring levels of phosphatase and/or prostate-specific antigen (PSA) and serum testosterone.

4.3 Contraindications

- Hypersensitivity to leuprorelin or other GnRH analogues or to poly (D,L-lactide).
- Treatment with LEUPROLIDE HEXAL 5 is not indicated in cases where carcinomas are shown to be hormonally independent.

- After surgical castration, LEUPROLIDE HEXAL 5 does not cause any further reduction in testosterone levels.

4.4 Special warnings and precautions for use

As would be expected with this class of medicine, development or aggravation of diabetes may occur; therefore, diabetic patients may require more frequent monitoring of blood glucose during treatment with LEUPROLIDE HEXAL 5.

Epidemiological data have shown that during androgen deprivation therapy changes in the metabolic condition (e.g. reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased risk for cardiovascular diseases may occur. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be appropriately monitored.

Hepatic dysfunction and jaundice with elevated liver enzyme levels have been reported with the use of leuprorelin acetate. Therefore, close observation should be made and appropriate measures taken if necessary.

Spinal fracture, paralysis and hypotension have been reported.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as LEUPROLIDE HEXAL 5. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Post-marketing reports of seizures have been observed in patients treated with leuprorelin acetate and these events have been reported in both children and adults, and in those with or without a history of epilepsy, seizure disorders or risk disorders for seizures.

In the initial stages of therapy, a transient rise in levels of testosterone, dihydrotestosterone and acid phosphatase may occur, but then regress over a period of 2 weeks. After 2 to 4 weeks, testosterone levels comparable to those observed after bilateral orchiectomy is achieved, which is maintained throughout the entire duration of treatment.

In some cases, the short-term rise in serum testosterone levels may be associated with a "flare" or exacerbation of the tumour growth resulting in temporary deterioration of the patient's condition. These symptoms usually subside on continuation of therapy. "Flare" may manifest itself as systemic or neurological symptoms (occurrence or potentiation of ostalgia, urinary tract obstruction and its sequelae, spinal cord compression, myasthenia in legs, lymphoedema).

In order to reduce the risk of “flare”, an anti-androgen may be administered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone and exacerbation of clinical symptomatology.

In the rare event of an abscess occurring at the injection site, testosterone level should be monitored as there may be inadequate absorption of leuprorelin from LEUPROLIDE HEXAL 5.

Patients with vertebral or cerebral metastases and/or those at risk of ureteric obstruction and/or spinal cord compression should be considered carefully and closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens. Should urological/neurological complications occur, these should be treated by appropriate specific measures.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss which, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture. Adjuvant administration of bisphosphonates may prevent bone demineralisation in patients at risk.

If an anti-androgen is used over a prolonged period, due attention should be paid to the contraindications and precautions associated with its extended use.

Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long-term clinical studies with leuprorelin acetate.

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 medicine 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 LEUPROLIDE HEXAL 5.

Response to LEUPROLIDE HEXAL 5 therapy can be monitored by measuring serum levels of testosterone, acid phosphatase and PSA (prostate specific antigen).

4.5 Interaction with other medicines and other forms of interaction

There are no known interactions with other medicines.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of LEUPROLIDE HEXAL 5 with medicine known to prolong the QT interval or medicine able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g.

amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicine, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

4.6 Fertility, pregnancy and lactation

LEUPROLIDE HEXAL 5 is intended only for use in male patients.

4.7 Effects on ability to drive and use machines

Visual disturbances, dizziness, tiredness and fatigue may occur. LEUPROLIDE HEXAL 5 may alter reactivity to such an extent that the ability to drive or operate machinery is impaired. This applies to an even greater extent when combined with alcohol.

4.8 Undesirable effects

Adverse reactions seen with LEUPROLIDE HEXAL 5 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

In cases where a "tumour flare" occurs after LEUPROLIDE HEXAL 5 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia. These symptoms subside on continuation of therapy.

Infections and infestations:

Frequent: Urinary tract infections

Blood and lymphatic system disorders:

Frequency unknown: Anaemia (reported in medicines of this class), thrombocytopaenia, leucopaenia

Immune system disorders:

Frequency unknown: Hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions)

Metabolism and nutrition disorders:

Frequent: Weight fluctuation, decreased appetite

Frequency unknown: Lipids abnormal, glucose tolerance abnormal

Psychiatric disorders:

Frequent: Insomnia, depression (see section 4.4), mood changes (long-term use)**

Less frequent: Mood changes (short-term use)**

** mood changes (long-term use: frequent and short-term use: less frequent)

Nervous system disorders:

Frequent: Headache (occasionally severe)

Less frequent: Dizziness, paraesthesia, pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma

Frequency unknown: Paralysis (see section 4.4), seizure

Eye disorders:

Frequency unknown: Visual impairment

Cardiac disorders:

Frequency unknown: Palpitations, electrocardiogram QT prolonged (see sections 4.4 and 4.5)

Vascular disorders:

Frequent: Hot flush

Frequency unknown: Pulmonary embolism, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Haemoptysis, interstitial lung disease

Gastrointestinal disorders:

Frequent**:** Nausea, vomiting

Less frequent: Diarrhoea

Hepatobiliary disorders:

Frequent**:** Hepatic function abnormal, liver function test abnormal (usually transient)

Frequency unknown: Jaundice

Skin and subcutaneous tissue disorders:

Frequent**:** Hyperhidrosis

Frequency unknown: Dermatitis, skin reaction, abnormal hair growth

Musculoskeletal, connective tissue and bone disorders:

Frequent**:** Bone pain, muscle weakness, arthralgia

Less frequent: Myalgia, weakness of lower extremities

Frequency unknown: Spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists

Renal and urinary disorders:

Frequent**:** Nocturia, dysuria

Frequency unknown: Haematuria, pollakiuria, micturition urgency, urinary tract obstruction

Reproductive system and breast disorders:

Frequent: Libido decreased, erectile dysfunction, testicular atrophy, gynaecomastia

Frequency unknown: Testicular pain

General disorders and administration site conditions:

Frequent: Fatigue, injection site reaction e.g. induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis, asthenia, oedema peripheral

Frequency unknown: Pyrexia, chills

Investigations:

Frequent: Prostatic specific antigen increased

Frequency unknown: Blood calcium increased, blood uric acid increased

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No case of overdose has been reported.

In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 21.10 Trophic hormones

5.1 Pharmacodynamic properties

LEUPROLIDE HEXAL 5 contains leuprorelin acetate, a synthetic nonapeptide 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. For their part, these hormones stimulate gonadal steroid synthesis.

Leuprorelin acetate - also described as an LHRH agonist – blocks LHRH receptors in the pituitary gland during long-term therapeutic administration, thereby causing them to be desensitised following an initial short-term stimulation (“down regulation”). As a result, reversible pituitary suppression of gonadotropin release occurs, followed by a decrease in testosterone levels, thereby affecting the growth of androgen dependent prostatic tissue which has undergone carcinomatous changes. This tissue is normally stimulated by dihydrotestosterone, which is produced by the reduction of testosterone in prostatic cells.

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

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 LH, FSH and DHT levels, with testosterone levels thereby reduced to within the bilateral orchiectomy range.

These changes mostly occur 2 to 3 weeks following initiation of therapy and are manifest throughout the entire duration of treatment. Hence, hormonal sensitivity of prostatic carcinomas and the potential therapeutic value of orchiectomy can also be investigated with leuprorelin acetate. It has been possible to maintain castrate testosterone levels following continuous administration of leuprorelin acetate over 5 years.

Leuprorelin acetate is inactive when given orally.

5.2 Pharmacokinetic properties

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 LEUPROLIDE HEXAL 5 biodegradable implant. The polymer is absorbed in the same way as surgical suture material.

Within 2 hours after subcutaneous single dose application LEUPROLIDE HEXAL 5, peak serum leuprorelin levels of 5216 pg/mℓ (5,2 ng/mℓ) have been measured.

The AUC during 3 months' treatment with LEUPROLIDE HEXAL 5, was 32,4 ng/mℓ*d. Detectable levels in serum are present for up to 182 days (26 weeks) after administration. The volume of distribution of leuprorelin is 36 litres in men; total clearance is 139,6 mℓ/min.

The pharmacokinetics of this product has not been determined in patients with hepatic or renal impairment.

5.3 Preclinical safety data

A teratogenic effect has been observed in rabbits, but not in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly (D,L-lactide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Leuprolide Hexal 5 is available in a single dose administration kit containing 1 (one) pre-filled syringe, sealed in an aluminium sachet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park

1619

8. REGISTRATION NUMBER

A40/21.10/0263

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 April 2016

10. DATE OF REVISION OF THE TEXT

10 September 2020

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Leuprolide Hexal 5	NS2	14/21.10/0049

ATC Code: A.21.10, Trophic hormones

Name and address of manufacturer:

EVER Pharma Jena GmbH,
Otto-Schott Srasse 15,
De-07745 Jena
Germany

[1]Company Reg. No.: 1990/001979/07