PROPOSED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

LEUPROLIDE HEXAL 5 (implant)

COMPOSITION:

Each Leuprolide Hexal 5 implant contains 5,25 mg leuprorelin acetate equivalent to 5 mg leuprorelin.

List of excipients*:*

Poly (D,L-lactide)

PHARMACOLOGICAL CLASSIFICATION:

A 21.10 Tropic hormones

PHARMACOLOGICAL ACTION:

Leuprorelin acetate 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. For their part, these hormones stimulate gonadal steroid synthesis.

Pharmacodynamic properties:

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.

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.

INDICATIONS:

Treatment of patients with advanced hormone-dependent prostate carcinoma.

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.

WARNINGS AND SPECIAL PRECAUTIONS:

Testosterone levels initially increase upon initiation of therapy, 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 are maintained throughout the entire duration of treatment.

The short-term rise in serum testosterone levels may lead to a transient intensification of certain clinical symptoms (occurrence or potentiation of ostalgia, urinary tract obstruction and its sequelae, spinal cord compression, myasthenia in legs, lymphoedema). Potentiation of complaints usually subsides spontaneously without any necessity to discontinue LEUPROLIDE HEXAL 5.

For this initial phase of treatment, adjuvant administration of an appropriate anti-androgen should be taken into consideration, in order to make any possible sequelae less severe (initial rise in testosterone and exacerbation of clinical symptomatology).

Patients with vertebral or cerebral metastases and/or those with urinary tract obstruction should be placed under particularly close monitoring, especially during the first weeks of treatment. Spinal cord compression and impaired renal function have been observed in such patients.

There may also be a rise in acid phosphatase levels during the initial phase of therapy, which is transient in nature. Normal values or almost normal values are generally re-achieved after a few weeks.

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

Hypogonadism occurring during long-term therapy with GnRH analogues may lead to osteoporosis with an elevated risk of fractures. Adjuvant administration of bisphosphonate may prevent bone demineralisation in patients at risk.

Special precaution should be taken in patients with a history of convulsions, seizures and cardiovascular problems.

Glucose metabolism may be impaired. Patients with diabetes mellitus should be monitored for changes in their glucose homeostasis.

Effects on ability to drive and use machines:

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.

INTERACTIONS:

There are no known interactions with other medicines.

PREGNANCY AND LACTATION:

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

DOSAGE AND DIRECTIONS FOR USE:

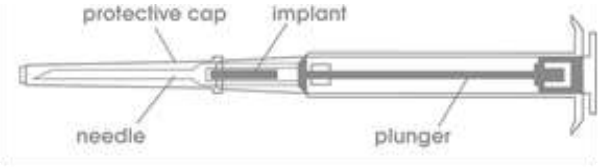
The recommended dose is a single dose of LEUPROLIDE HEXAL 5 once every 12 weeks.

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 “Pharmacokinetic properties”).

Method of administration:

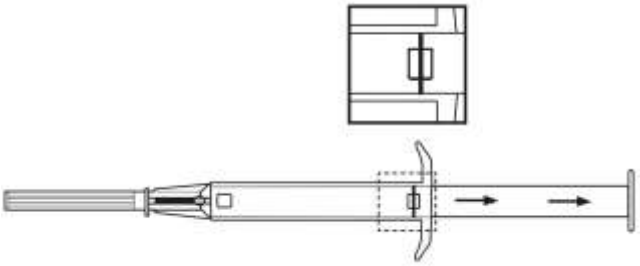
Application should be performed by a medical practitioner experienced in tumour therapy. The implant is inserted subcutaneously into the abdominal skin.

Directions for use:



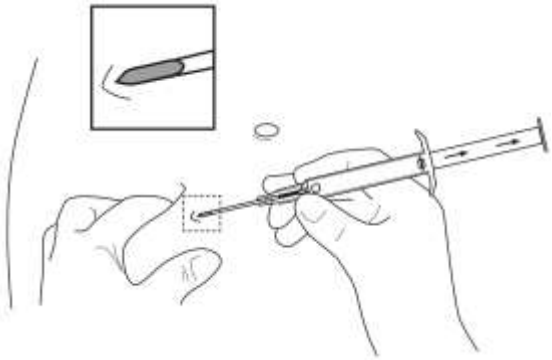
1. Disinfect the injection site on the anterior abdominal wall below the navel line.
2. Remove the syringe from the sterile bag and check that the implant is visible in the repository (see framed area). For verifying, view the syringe against a light or gently shake it.
3. Pull the plunger of the syringe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

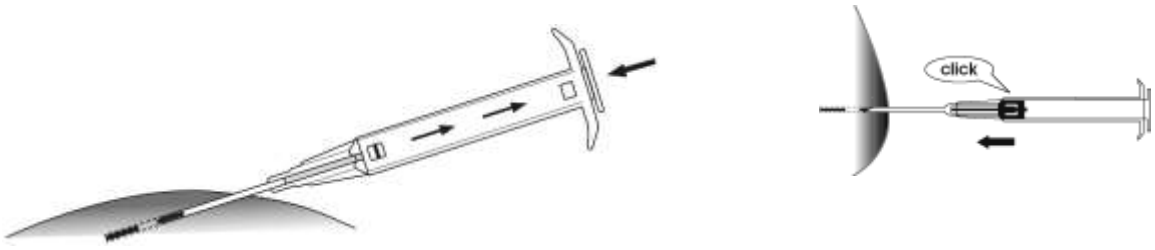


4. Remove the protective cap from the needle.

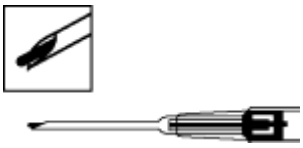
5. Hold the main body of the syringe with one hand. With the other hand pinch the patient's skin of the anterior abdominal wall below the navel line. See illustration. With the **needle opening facing upwards, insert the whole needle.** Do this at a slight angle, almost parallel to the skin into the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

SIDE EFFECTS:

Infections and infestations:

Frequent: Urinary tract infections.

Metabolism and nutrition disorders:

Frequent: Anorexia.

The following has been reported but frequency is unknown: Diabetes mellitus.

Psychiatric disorders:

Frequent: Decreased libido.

The following has been reported but frequency is unknown: Insomnia.

Nervous system disorders:

The following has been reported but frequency is unknown: Paraesthesia.

Cardiac disorders:

The following has been reported but frequency is unknown: Angina pectoris, dysrhythmia.

Vascular disorders:

Frequent: Hot flushes.

Respiratory, thoracic and mediastinal disorders:

***Frequent*:** Dyspnoea.

The following has been reported but frequency is unknown: Haemoptysis.

Gastrointestinal disorders:

***Frequent*:** Nausea, vomiting.

The following has been reported but frequency is unknown: Diarrhoea.

Skin and subcutaneous tissue disorders:

***Frequent*:** Hyperhidrosis, pruritus.

The following has been reported but frequency is unknown: Dermatitis, skin reaction, abnormal hair growth.

Musculoskeletal, connective tissue and bone disorders:

***Frequent*:** Bone pain, muscular weakness.

The following has been reported but frequency is unknown: Myalgia.

Renal and urinary disorders:

***Frequent*:** Nocturia, dysuria.

The following has been reported but frequency is unknown: Haematuria, pollakiuria, micturition urgency.

Reproductive system and breast disorders:

Frequent: Erectile dysfunction, testicular disorder.

The following has been reported but frequency is unknown: Gynaecomastia, testicular pain.

General disorders and administration site conditions:

Frequent: Reactions at the injection site e.g. reddening at the site of injection, fatigue, oedema, pain, asthenia.

The following has been reported but frequency is unknown: Pyrexia, chills, nodule.

Investigations:

Frequent: Weight increased, prostatic specific antigen increased.

The following has been reported but frequency is unknown: Blood calcium increased, blood uric acid increased.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See “SIDE EFFECTS”.

No symptoms of intoxication have been observed to date. Treatment is symptomatic and supportive.

IDENTIFICATION:

Leuprolide Hexal 5: White to slightly yellowish implant with an uniform surface, one implant in each syringe, sealed in a sachet.

PRESENTATION:

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

STORAGE INSTRUCTIONS:

Store at room temperature (at or below 25 °C).

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/21.10/0263

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park

1619

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 21 April 2016

Date of most recent approval of professional information: 06 April 2017

Additional country registration details:

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

Name and address of manufacturer:

EVER Pharma Jena GmbH

Otto-Schott Strasse 15, DE - 07745 Jena,

Germany

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