PRODUCT MONOGRAPH

PrZEULIDE DEPOT™

Leuprolide acetate for depot suspension
3.75 mg [1-Month]
22.5 mg [3-Month]

(for administration upon reconstitution)

Luteinizing Hormone-Releasing Hormone (LH-RH) Analog

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Date of Revision:
August 14, 2018

Submission Control No: 217418

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PrZEULIDE DEPOT™
Leuprolide acetate for depot suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Intramuscular	Lyophilized powder for injection (suspension after reconstitution with diluent) ▪ 3.75 mg [1-Month] (5.06 mg/vial to deliver 3.75 mg leuprolide acetate) ▪ 22.5 mg [3-Month] (28.13 mg/vial to deliver 22.5 mg leuprolide acetate)	3.75 mg [1-Month]: Mannitol, poly (D, L-lactide-co-glycolide), polysorbate 80 and triethyl citrate 22.5 mg [3-Month]: Mannitol, polylactic acid, polysorbate 80 and triethyl citrate *For a complete listing see **Dosage Forms, Composition and Packaging** section.*

INDICATIONS AND CLINICAL USE

ZEULIDE DEPOT (leuprolide acetate for depot suspension) is indicated for the palliative treatment of advanced and/or metastatic prostate cancer.

ZEULIDE DEPOT must be administered under the supervision of a health care professional.

Geriatrics (> 65 years of age)
The majority of the patients studied in the clinical trials for ZEULIDE DEPOT were 65 years and older (mean age of 71 ± 9 years) (see CLINICAL TRIALS).

Pediatrics (< 12 years of age)
The safety and effectiveness of ZEULIDE DEPOT in pediatric patients have not been established (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

- ZEULIDE DEPOT is contraindicated in patients with hypersensitivity to luteinizing hormone-releasing hormone (LH-RH), LH-RH analogs or any of the components of ZEULIDE DEPOT. Anaphylactic reactions to synthetic LH-RH or LH-RH analogs have been reported in literature. For a complete listing, see the DOSAGE FORMS,

COMPOSITION AND PACKAGING section.

- ZEULIDE DEPOT is contraindicated in women, especially those who are or may become pregnant while receiving the drug. There are possibilities that fetal harm and spontaneous abortions may occur.
- The use of ZEULIDE DEPOT in nursing mothers is contraindicated.
- ZEULIDE DEPOT is not indicated in pediatric patients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZEULIDE DEPOT should be prescribed by a qualified physician experienced in the use of hormonal therapy in prostate cancer.

The following are clinically significant adverse events:

- Clinical testosterone flare reaction in men with prostate cancer (See General below)
- Osteoporosis (See Endocrine and Metabolism below)
- Sudden cardiac deaths (See Cardiovascular below)
- Pituitary Apoplexy (See Post-Market Adverse Drug Reactions below)
- Drug-induced Liver Injury (See Hepatic/Biliary/Pancreatic below)

General

ZEULIDE DEPOT, like other LH-RH analogs, causes a transient increase in serum concentration of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH analogs. If spinal cord compression or renal impairment due to urethral obstruction develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin leuprolide acetate therapy under close supervision.

Carcinogenesis and Mutagenesis

Two-year carcinogenicity studies were conducted with leuprolide acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas were noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumours or pituitary abnormalities were observed at a dose as

high as 60 mg/kg for two years.

Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities. No carcinogenicity studies have been conducted with ZEULIDE DEPOT.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Cardiovascular

There may be a relationship between androgen deprivation therapy and cardiovascular risk in men with prostate cancer on the basis of the demonstrated adverse impact of androgen deprivation on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Reports of events related to cardiovascular ischemia including myocardial infarction, stroke, cardiovascular-related, and sudden cardiac deaths have been received in patients treated with LH-RH agonists.

Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential cardiovascular risk. Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered (see Monitoring and Laboratory Tests below).

Effect on QT/QTc interval

Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g., quinidine, procainamide), Class III (e.g., amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g., flecainide, propafenone) antiarrhythmic medications (see DRUG INTERACTIONS).

In a randomized, active-controlled trial to compare leuprolide acetate 7.5 mg with a LH-RH antagonist in patients with prostate cancer, periodic electrocardiograms were collected. The analysis of the pooled data in the leuprolide cohort (N=46 patients) showed a mean QTcF increase of 17 msec from baseline; the percentage of subjects who experienced a QTcF change of ≥ 30 msec and ≥ 60 msec from baseline was 41% (N=19 patients) and 4% (N=2 patients), respectively.

Dependence/Tolerance

No drug-dependence has been reported with the use of leuprolide acetate.

Endocrine and Metabolism

Changes in bone density

Decreased bone mineral density can be anticipated with long-term use of an LH-RH agonist. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone

fractures. The risk of skeletal fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.
In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, leuprolide acetate may pose an additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with ZEULIDE DEPOT is instituted.

Hypogonadism
Long-term administration of leuprolide acetate will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Reduction in glucose tolerance
A reduction in glucose tolerance and an increased risk in developing diabetes have been reported in men treated with androgen deprivation therapy. Patients treated with LH-RH agonists should undergo periodic monitoring of blood glucose. Diabetic patients may require more frequent monitoring when receiving LH-RH agonists.

Hematologic

Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered. Leuprolide acetate should be used with caution in patients with known bleeding disorders, thrombocytopenia or on treatment with anticoagulants.

Hepatic/Biliary/Pancreatic

Hepatic dysfunction and jaundice with elevated liver enzyme levels have been reported with the use of leuprolide acetate. Postmarketing reports of serious drug-induced liver injury have been observed in patients on leuprolide acetate therapy.

The pharmacokinetics of the drug in patients with hepatic, biliary or pancreatic impairment have not been determined.

Neurologic

Postmarketing reports of convulsion have been observed in patients on leuprolide acetate therapy.

Psychiatric

Like other drugs in this class, mood swings, including depression, have been reported with leuprolide acetate therapy. There have been reports of suicidal ideations and attempt. Patients

should be counseled on the possibility of development or worsening of depression during treatment with leuprolide acetate.

Renal

The pharmacokinetics of the drug in patients with renal impairment have not been determined.

Respiratory

The following adverse effects have been reported with the use of leuprolide acetate injection: chest tightness decreased breathing sounds, hemoptysis, pleuritic chest pain, pulmonary infiltrate, rales/rhonchi, rhinitis, strep throat, and wheezing/bronchitis.

Sexual Function/Reproduction

Sexual dysfunction (14%) with decrease in libido and impotence were reported with the use of leuprolide acetate.

Special Populations

Pregnant women
ZEULIDE DEPOT is contraindicated in women, especially those who are or may become pregnant while receiving the drug as it may cause fetal harm when administered to a pregnant woman.

Nursing women
ZEULIDE DEPOT is contraindicated in nursing women as safety and effectiveness have not been established in this group of patients.

Pediatrics (< 12 years of age)
ZEULIDE DEPOT is not indicated in children as safety and effectiveness have not been established in this group of patients.

Geriatrics (> 65 years of age)
The majority of the patients studied in clinical trials for ZEULIDE DEPOT were 65 years and older (mean age of 71 ± 9 years).

Effects on Ability to Drive and Use Machines
The ability to drive and use machines may be impaired due to visual disturbances and dizziness.

Monitoring and Laboratory Tests

Periodic renal function tests, ECG, electrolytes, and liver function tests are recommended.
Renal function tests, blood urea nitrogen (BUN) and creatinine may rarely be elevated during the first few days of therapy in prostate cancer patients before returning to normal. In clinical trials with leuprolide acetate however, no significant difference was observed from baseline to 7 days

following injection in terms of the number of patients who demonstrated an elevation from normal to above normal levels of creatinine and BUN.

The response to ZEULIDE DEPOT should be monitored periodically by measuring serum concentrations of testosterone and prostate-specific antigen (PSA). Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

The effects of leuprolide acetate on bone lesions may be monitored by bone scans, while its effects on prostatic lesions may be monitored by ultrasonography and/or computed tomography (CT) scan in addition to digital rectal examination. Intravenous pyelogram, ultrasonography, or CT scan may also be utilized to diagnose or assess the status of obstructive uropathy.

Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving ZEULIDE DEPOT should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording, and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QTc prolongation.

Blood glucose levels and/or glycosylated hemoglobin (HbA1c) should be checked periodically in patients treated with LH-RH agonists and more frequently in diabetic patients (see WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of ZEULIDE DEPOT was based on results from two Phase III clinical trials evaluated in a total of 323 patients with prostate cancer treated for 6 months (160 patients were treated with 3.75 mg injection administered every month and 163 patients were treated with 22.5 mg injection administered every 3 months).

ZEULIDE DEPOT, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first week of treatment. Therefore, potential exacerbation of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see WARNINGS AND PRECAUTIONS).

In the pivotal studies, 29 (18.1%) and 24 (14.7%) patients experienced local adverse events for the 3.75 mg and the 22.5 mg strengths, respectively, most of which were mild in severity. Local adverse events reported after injection of ZEULIDE DEPOT 3.75 mg (1-Month) and ZEULIDE DEPOT 22.5 mg (3-Month) were typical of those frequently associated with similar products administered via intramuscular route (i.m.). Those reported with ZEULIDE DEPOT 3.75 mg included pain at the site of injection (8.1%), irritation (4.4%) and discomfort (1.9%); those reported

with ZEULIDE DEPOT 22.5 mg included injection site pain (10.4%), injection site erythema (3.1%) and injection site induration (2.5%). Other less frequently reported local adverse events included erythema/bruising (1.3% each), injection site reaction/ swelling/ injury/ haemorrhage (0.6% each) with ZEULIDE DEPOT 3.75 mg, and injection site discomfort/ hemorrhage/ urticaria/ warmth, vessel puncture site pain, arthralgia and musculoskeletal pain (0.6% each) with ZEULIDE DEPOT 22.5 mg.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following possibly or probably related systemic adverse reactions were reported by ≥ 2% of the patients who were administered ZEULIDE DEPOT 3.75 mg [1 injection every month] and 22.5 mg [1 injection every 3 months] in the pivotal studies for a total of 6 months (Table 1).

Table 1: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 2% of Patients Treated with ZEULIDE DEPOT 3.75 mg and ZEULIDE DEPOT 22.5 mg for up to 6 Months

Body System Adverse Event	**ZEULIDE DEPOT 3.75 mg N=160 (%)**	**ZEULIDE DEPOT 22.5 mg N=163 (%)**
Vascular disorder		
Hot flashes*	72 (45.0)	126 (77.3)
General disorders and administration site conditions		
Asthenia	-	7(4.3)
Fatigue	10 (6.3)	16 (9.8)
Injection site erythema	-	5 (3.1)
Injection site induration	-	4 (2.5)
Injection site pain	-	15 (9.2)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	6 (3.8)	5 (3.1)
Night sweats*	5 (3.1)	-
Investigations		
Alanine aminotransferase increased	-	4 (2.5)
Gastrointestinal disorders		
Nausea	-	4 (2.5)
Musculoskeletal and connective tissue disorders		
Bone pain	-	4 (2.5)
Nervous system disorders		
Headache	5 (3.1)	-
Psychiatric disorders		
Insomnia	-	4 (2.5)
Renal and urinary disorders		
Pollakuria	-	4 (2.5)

* Expected pharmacological consequence of testosterone suppression

Hot flashes were the most common adverse event reported (45% of patients in ZEULIDE DEPOT

3.75 mg and 77.3% in ZEULIDE DEPOT 22.5 mg). As reported in the ZEULIDE DEPOT 3.75 mg clinical trial, hot flashes were severe in 2 patients (1.3%), moderate in 10 patients (6.3%) and mild in 64 patients (40%). In the ZEULIDE DEPOT 22.5 mg clinical trial, hot flashes were reported as severe in 5 patients (3.1%), moderate in 28 patients (17.2%), and mild in 94 patients (57.7%).

Less Common Clinical Trial Adverse Drug Reactions (<2%)

The following possibly or probably related systemic adverse events were reported by <2% of the patients treated with ZEULIDE DEPOT 3.75 mg and ZEULIDE DEPOT 22.5 mg in clinical studies.

ZEULIDE DEPOT 3.75 mg (1-Month)

Ear and labyrinth disorders:	Vertigo
Gastrointestinal disorders:	Abdominal pain lower, diarrhea, nausea, vomiting
General disorders and administration site conditions:	Asthenia, feeling hot and cold, feeling jittery, pyrexia
Hepatobiliary disorders:	Hyperbilirubinemia
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, body temperature increased, gamma-glutamyltransferase increased
Metabolism and nutrition disorders:	Anorexia, hypercholesterolemia, hyperlipidemia, increased appetite
Musculoskeletal and connective tissue disorders:	Arthralgia, back pain, muscle spasms, pain in extremity
Nervous system disorders:	Somnolence
Psychiatric disorders:	Insomnia, libido decreased*, mood altered, sleep disorder
Renal and urinary disorders:	Pollakiuria, urinary incontinence, urinary retention
Reproductive and breast disorders:	Breast swelling*, breast tenderness, ejaculation failure*, erectile dysfunction*
Skin and subcutaneous tissue disorders:	Cold sweat*, periorbital edema, pruritus, urticaria

* Expected pharmacological consequences of testosterone suppression

ZEULIDE DEPOT 22.5 mg (3-Month)

Ear and labyrinth disorders:	Tinnitus
Eye disorders:	Vision blurred
Gastrointestinal disorders:	Abdominal pain upper, constipation, diarrhea
General disorders and administration site conditions:	Adverse drug reaction, cold sweat, feeling hot, hyperhidrosis, injection site discomfort/hemorrhage/urticaria/warmth, pain, vessel puncture site pain
Investigations	Aspartate aminotransferase increased, blood calcium increased, blood creatinine increased, blood lactate dehydrogenase increased, blood creatinine phosphokinase increased, blood glucose increased, blood potassium decreased, blood potassium increased, blood triglyceride increased, blood urea increased, ECG QT prolonged, ECG QT shortened, ECG T wave inversion, Eastern Cooperative Oncology Group (ECOG) status worsened, gamma-glutamyltransferase increased, glomerular filtration rate decreased, hematocrit decreased, hematology test abnormal, hemoglobin decreased, mean cell volume increased, red blood cell count decreased, residual urine volume increased
Metabolism and nutrition disorders:	Decreased appetite, hypercholesterolemia
Musculoskeletal and connective tissue disorders:	Arthralgia, back pain, musculoskeletal pain, neck pain
Nervous system disorders:	Dizziness, dysgeusia, formication, headache, lethargy
Psychiatric disorders:	Anger, anxiety, depression, emotional disorder, libido decreased, sleep disorder
Renal and urinary disorders	Nocturia, urinary tract pain, urine flow decreased
Reproductive system and breast disorders:	Erectile dysfunction*, nipple pain, pelvic pain, testicular atrophy, testicular disorder
Respiratory, thoracic and mediastinal disorders	Pleurisy
Skin and subcutaneous tissue disorders:	Cold sweat*, night sweats, papule, pruritus, pruritus generalised, rash
Vascular disorder	Flushing

* Expected pharmacological consequences of testosterone suppression

ECOG: Eastern Cooperative Oncology Group

Abnormal Hematologic and Clinical Chemistry Findings

Abnormalities of certain parameters were observed, but are difficult to assess in this population. For ZEULIDE DEPOT 22.5 mg, the following value was observed in ≥ 2% of patients: alanine aminotransferase (ALT) increased. A number of abnormal values judged as clinically significant (each < 2%) were observed for some laboratory parameters in both ZEULIDE DEPOT clinical trials (see Less Common Clinical Trial Adverse Drug Reactions, Investigations).

Post-Market Adverse Drug Reactions

Changes in Bone Density
Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy
During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of LH-RH agonists. In the majority of these cases, a pituitary adenoma was diagnosed, with most of the pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Convulsions
During post-marketing surveillance, which includes other dosage forms and other patient populations, convulsions were reported in patients on leuprolide acetate therapy.

Hepatic and renal insufficiency
Post-marketing reports of serious drug-induced liver injury have been observed in patients on leuprolide acetate therapy.

DRUG INTERACTIONS

Overview

No formal drug interaction studies have been conducted with ZEULIDE DEPOT. No data is available on the interaction with alcohol.

Drug-Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of leuprolide acetate with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to the examples that follow: Class IA (e.g., quinidine, disopyramide), Class III (e.g., amiodarone, dronedarone, sotalol, dofetilide, ibutilide), or Class IC (e.g., flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g., chlorpromazine), antidepressants (e.g., amitriptyline, nortriptyline), opioids (e.g., methadone), macrolide antibiotics and analogs (e.g., erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g., moxifloxacin), antimalarials (e.g., quinine), azole antifungals, 5-hydroxytryptamine (5-HT3)

receptor antagonists (e.g., ondansetron), and beta-2 adrenoceptor agonists (e.g., salbutamol).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Therapy with leuprolide acetate results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide therapy may be affected.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- ZEULIDE DEPOT must be administered under the supervision of a health care professional.

- ZEULIDE DEPOT 3.75 mg and 22.5 mg administered intramuscularly is designed to provide continuous sustained-release of leuprolide for 1 and 3 months, respectively.

Recommended Dose and Dosage Adjustment

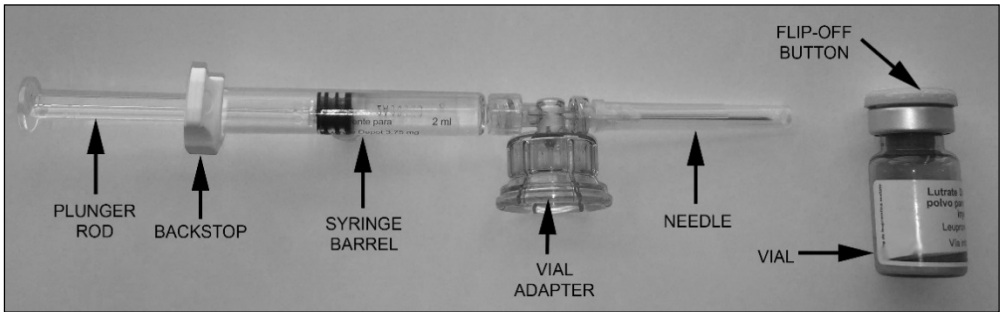
ZEULIDE DEPOT 3.75 mg (1-Month)
The recommended dose of ZEULIDE DEPOT (1-Month) is 3.75 mg administered monthly as a single intramuscular injection, after reconstitution with the ready-to-use diluent.

ZEULIDE DEPOT 22.5 mg (3-Month)
The recommended dose of ZEULIDE DEPOT (3-Month) is 22.5 mg administered once every 3 months as a single intramuscular injection, after reconstitution with the ready-to-use diluent.

Missed Dose

Maintaining testosterone suppression is important in treating the symptoms of hormone-dependent prostate cancer. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of ZEULIDE DEPOT injection is an important part of treatment.

Administration



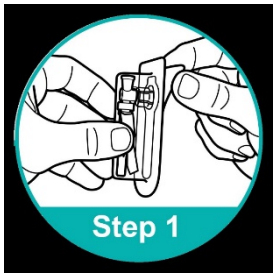
The ZEULIDE DEPOT microsphere powder contained in the vial should be reconstituted with the ready-to-use diluent provided in the syringe immediately prior to administration of vial contents by intramuscular injection. Make sure an aseptic technique is followed.

No other diluent can be used for reconstitution of ZEULIDE DEPOT.

The product must be brought to room temperature before administration. Some product may cake or clump at the vial wall. This is considered normal. The vial is filled with excess product for the 1-Month (35% overfill) and 3-Month (25% overfill) formulations in order to make sure that a final dose of 3.75 mg and 22.5 mg of leuprolide acetate is administered, respectively.
The product is meant for a single injection. Any remaining solution must be discarded.

Reconstitute ZEULIDE DEPOT according to the following instructions:

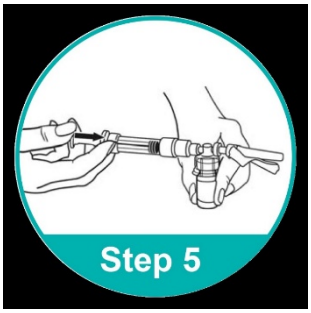
Remove (i) the blue cap from the vial, (ii) the grey cap from the syringe barrel and then (iii) the blister pack from the vial adapter (Step 1).



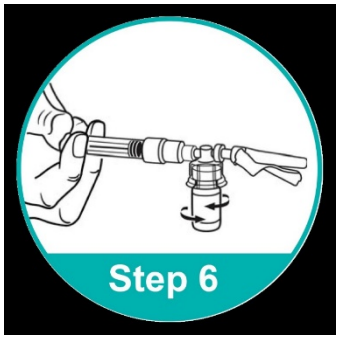
Attach the adapter system to the vial until a “clicking” sound is heard (Steps 2 and 3).

Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter (Step 4). Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

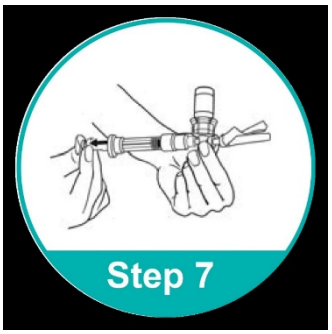
While keeping the syringe and vial securely coupled in an upright position, slowly push the plunger in order to transfer all the diluent into the vial (Step5).



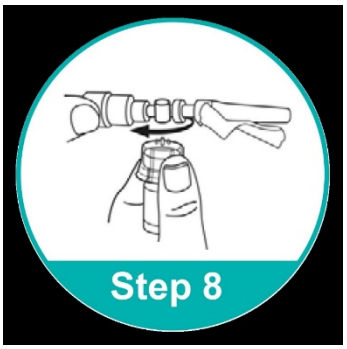
With the syringe still coupled to the vial, shake the vial gently for approximately one minute until a uniform milky-white suspension is obtained (Step 6).



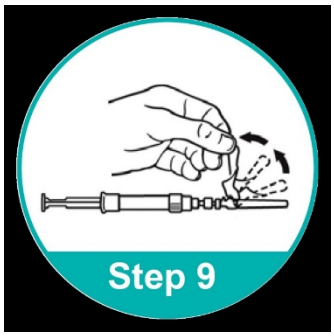
Turn the system upside down, and carefully pull out the plunger to absorb the resuspended drug contained within the vial (Step 7).

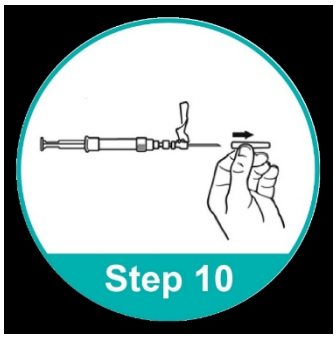


Detach the syringe from the adaptor system by twisting the upper piece of the adaptor counter-clockwise (Step 8). The drug is ready to be used.

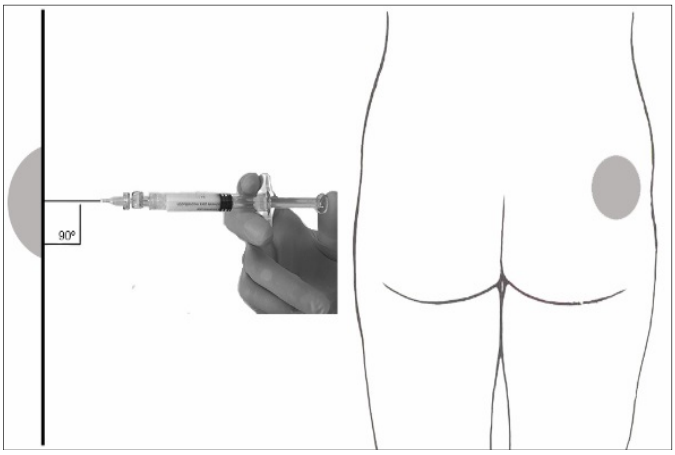


Lift up the safety cover (Step 9) and remove the clear plastic needle shield by pulling it from the assembly (Step 10). The safety cover should be perpendicular to the needle, with the needle facing away from you.





Clean the injection area with an alcohol swab and let the skin dry. Inject the suspension intramuscularly into the upper outer quadrant of the gluteus.



NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock. If blood is present, remove the needle immediately. Do not inject the medication.

After injecting the product, immediately activate the safety mechanism by centering your thumb or forefingers on the textured finger pad area of the safety cover and pushing it forward over the needle until you hear or feel it locked (Step 11).

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose. Because the acute animal toxicity of the drug is low, adverse effects are not expected. No difference in adverse reactions was observed in patients who received either 1 or 10 mg/day of leuprolide acetate for up to three years or 20 mg/day for up to two years.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Leuprolide acetate is a synthetic nonpeptide analog of naturally-occurring luteinizing hormone-releasing hormone (LH-RH). The analog possesses greater potency than the natural hormone. When administered as indicated, leuprolide acetate acts as a potent inhibitor of gonadotropin production. It is chemically unrelated to steroids.

Unlike steroid hormones, leuprolide acetate exerts specific action on the pituitary gonadotrophs and the human reproductive tract.

This specificity reduces the likelihood of secondary adverse effects such as gynecomastia, thromboembolism, oedema, liver and gallbladder involvement.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in the levels of the gonadal steroids (testosterone and dihydrotestosterone in males and oestrone and estradiol in premenopausal females). However, continuous administration results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and are maintained as long as treatment continues. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to 5 years. The effect is reversible upon discontinuation of drug therapy.

Pharmacodynamics

The pharmacodynamic (PD) response following three monthly injections of ZEULIDE DEPOT 3.75 mg was evaluated in 12 patients with advanced prostate cancer. Following the first administration (Month 1, Days 0 – 28), leuprolide concentrations increased rapidly. The first peak was followed by a decline and then by a further increase of the drug levels caused by sustained release of leuprolide. In response to this pattern of leuprolide exposure, mean testosterone levels rapidly increased from baseline levels (reaching peak levels by Day 3), and then fell to below castrate levels (≤ 0.5 ng/mL) within 21 days after the first dose. All patients who completed the study maintained castrate levels at all monthly assessments.

For ZEULIDE DEPOT 22.5 mg, the PD response was evaluated following two injections 3 months apart in 30 patients with prostate cancer. Similar to the 3.75 mg formulation, following each drug administration, leuprolide concentrations increased rapidly to a peak value and then declined over the next several days, after which sustained release of leuprolide was maintained. In response to this pattern of leuprolide exposure, mean testosterone levels rapidly increased from baseline levels (reaching peak levels on Day 2), and then fell to below castrate levels (≤ 0.5 ng/mL) by Day 28. After the second administration on Day 84, the PD parameters for testosterone reflected very low or below the limit of quantification plasma concentrations and castrate levels were maintained for the duration of the study (Day 168).

Pharmacokinetics

Absorption
Following three monthly injections of ZEULIDE DEPOT 3.75 mg in a sample of prostate cancer patients (N=12), maximal leuprolide acetate plasma concentration was similar among the three cycles. After the first injection (Month 1, Days 0-28), an initial burst phase characterized by high leuprolide concentration (C_{max} was 13.14 ± 3.07 ng/mL at 0.04 days) was followed by a decrease in leuprolide levels and by a second rise characterized by a plateau phase during which leuprolide concentrations remained relatively constant.

In a pharmacokinetic (PK) study conducted with two sequential injections (3 months apart) of ZEULIDE DEPOT 22.5 mg in a sample of prostate cancer patients (N=30), maximal leuprolide acetate plasma concentration was similar after each drug administration. An initial burst phase, characterized by high leuprolide concentration was observed following the first injection (C_{max} was 6.66 ± 3.40 ng/mL at Day 2). The leuprolide peak was followed by a decline in leuprolide concentrations with plateau levels being maintained until the following dose on Day 84; a similar response was observed following the next drug administration. Maximum plasma concentrations of leuprolide (C_{max}) for Days 0 to 84 (Dose 1) and Days 84 to 168 (Dose 2) corresponded to mean (± SD) 46.79 (± 18.0) ng/mL and 48.30 (± 18.6) ng/mL, respectively. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

There was no evidence of leuprolide accumulation after repeated administration of ZEULIDE DEPOT at both strengths.

Distribution
The mean steady-state volume of distribution of leuprolide acetate following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism
In healthy male volunteers, a 1 mg bolus of leuprolide acetate administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model. The major metabolite of leuprolide is a pentapeptide (M-1) metabolite. No drug metabolism study was conducted with ZEULIDE DEPOT.

Excretion:
No drug excretion study was conducted with ZEULIDE DEPOT.

Special Populations and Conditions

Pediatrics
The safety and effectiveness of ZEULIDE DEPOT in paediatric patient have not been established.

Geriatrics

The majority of the patients studied in ZEULIDE DEPOT clinical trials were aged 65 and older (mean age of 71 ± 9 years).

Gender
ZEULIDE DEPOT is contraindicated in females.

Hepatic and renal insufficiency
Hepatic dysfunction and jaundice with elevated liver enzyme levels have been reported with the use of leuprolide acetate. Post-marketing reports of serious drug-induced liver injury have been observed in patients on leuprolide acetate therapy.

The pharmacokinetics of the drug in hepatic and renal impaired patients has not been determined.

Genetic Polymorphism
The effect of genetic polymorphism on the pharmacokinetics of ZEULIDE DEPOT was not studied.

STORAGE AND STABILITY

ZEULIDE DEPOT must be stored below 25ºC in the original package in order to protect from light. Protect from freezing.

Once reconstituted with the diluent, the suspension should be administered immediately. Any remaining solution must be discarded.

SPECIAL HANDLING INSTRUCTIONS

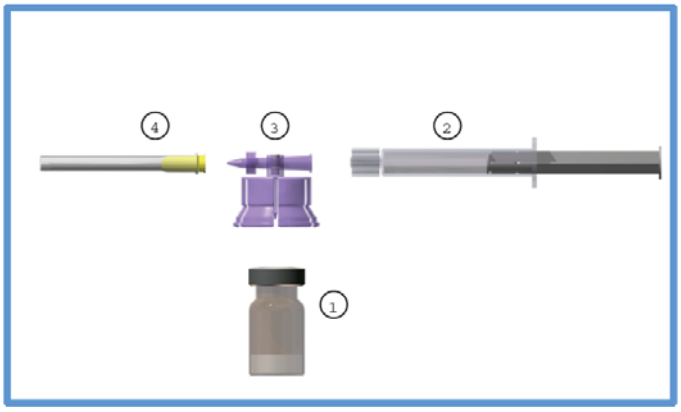
Allow the product to reach room temperature before using.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZEULIDE DEPOT (leuprolide acetate for depot suspension) a microencapsulated, sustained-release formulation of leuprolide acetate is supplied in single dose kits containing (1) one vial of medicinal ingredient, (2) one prefilled syringe containing 2 mL of diluent, (3) one adaptor system, and (4) one sterile 21G needle.

ZEULIDE DEPOT 3.75 mg (1-Month): Contains one vial of 5.06 mg of lyophilized leuprolide acetate (35% overfill) to deliver 3.75 mg of leuprolide acetate upon reconstitution and withdrawal. The vial contains the following non-medicinal ingredients (alphabetically): mannitol, poly (D, L-lactide-co-glycolide) (PLGA) 50/50, polysorbate 80, sodium carboxymethylcellulose and triethyl citrate.

ZEULIDE DEPOT 22.5 mg (3-Month): Contains one vial of 28.13 mg of lyophilized leuprolide acetate (25% overfill) to deliver 22.5 mg of leuprolide acetate upon reconstitution and withdrawal. The vial contains the following non-medicinal ingredients (alphabetically): mannitol, polylactic acid, polysorbate 80, sodium carboxymethylcellulose and triethyl citrate.



The prefilled syringe contains 2 mL of diluent that is composed of the following non-medicinal ingredients (alphabetically): 0.8% w/v mannitol, water for injection. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

When mixed with diluent, the sterile lyophilizate becomes a suspension, which is intended as an intramuscular injection to be given once every month (3.75 mg), or every three months (22.5 mg).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

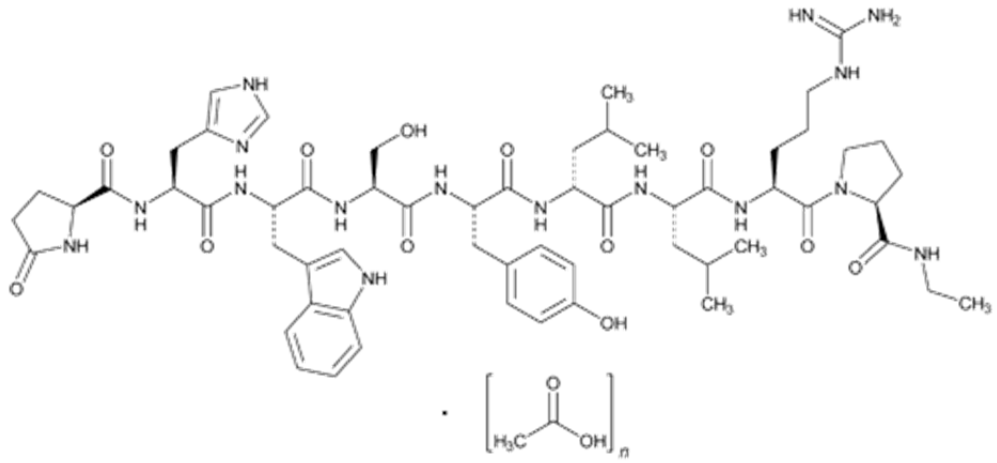
Proper name: Leuprolide acetate

Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-Leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Molecular formula: $C_{59}H_{84}N_{16}O_{12}\cdot C_2H_4O_2$

Molecular mass: 1209.41 as free base

Structural formula:



Physicochemical properties

Description: Leuprolide acetate is a fine or fluffy, white to off-white powder.

Solubility: Very soluble in water, ethanol and propylene glycol

pKa: 9.6

CLINICAL TRIALS

Summary of Patient Demographics in the Phase III Clinical Trials

Parameter	ZEULIDE DEPOT 3.75 mg Safety Population (N=160)	ZEULIDE DEPOT 22.5 mg Safety Population (N=163)
Age		
Mean ± SD	71.6 ± 9.2	71.0 ± 9.0
Range	48-90	47-91
Weight (kg)		
Mean ± SD	83.7 ± 15.5	88.8 ± 18.6
Range	51-130	52-159
Height (cm)		
Mean ± SD	174.2 ± 8.1	175.0 ± 8.0
Range	150-193	149-191
Sex		
Male	160 (100%)	163 (100%)
Race		
Caucasian	140 (87.5%)	101 (62.0%)
Black	16 (10%)	49 (30.1%)
Hispanic	3 (1.9%)	9 (5.5%)
Asian		2 (1.2%)
Other	1 (0.6%)	2 (1.2%)
Baseline Testosterone (ng/mL)		
Mean ± SD	5.48 ± 4.20	4.14 ± 1.83
Range	1.33-30.70	0.63-9.90

Study Results

Two Phase III open-label, multicentre studies were conducted to evaluate the safety and efficacy of ZEULIDE DEPOT in prostate cancer patients.

The first study was carried out to determine whether ZEULIDE DEPOT 3.75 mg injected intramuscularly once every four weeks for 24 weeks would reduce testosterone to, and maintain it at castrate levels (≤ 0.5 ng/mL) in 160 previously untreated prostate cancer patients.

By Day 21, 78.7% of the patients had achieved medical castration. By Day 28, 96.8% of the patients had achieved castrate levels and 73.1% had achieved levels of ≤ 0.2 ng/mL. No breakthrough or acute-on-chronic responses were reported throughout the study. Every patient involved in the study (100%) maintained castrate levels at all the key time-points (Days 56, 84, 112, 140 and 168) until the end of the study (see Figure 1). At the end of the study, 92.8% of the patients had testosterone levels ≤ 0.2 ng/mL.

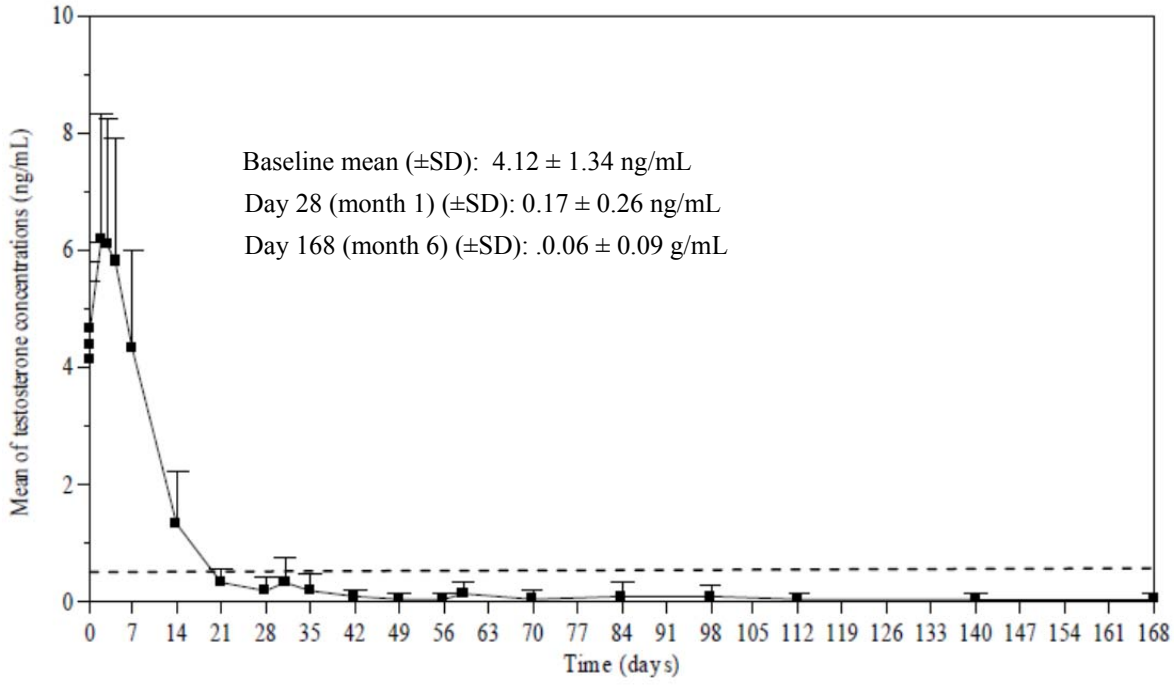


Figure 1: Plasma Testosterone Concentrations (Mean ± SD) for All Patients (N=160) Who Received 6 Monthly i.m. Injections of ZEULIDE DEPOT 3.75 mg

By Day 14 and Day 4 after the first ZEULIDE DEPOT injection, mean LH and FSH serum levels had decreased below the baseline concentrations, respectively. In addition, mean serum PSA levels gradually decreased during the first month and then remained constantly below baseline levels until the end of the study. However, a wide inter-individual variation in PSA concentrations was observed throughout the study.

Next, a multiple-dose study was carried out to evaluate two sequential doses of ZEULIDE DEPOT 22.5 mg administered in a 3-month interval to 163 patients with histologically proven carcinoma of the prostate. Testosterone levels were suppressed below the castrate threshold (≤0.5 ng/mL) in 98.7% of the patients by Day 28. Additionally, 78.0% of the patients achieved the more stringent criterion of testosterone ≤0.2 ng/mL at this time. At the end of the study (Day 168), 99.3% patients maintained castrate levels. Additionally, 90.7% of the patients presented testosterone levels ≤0.2 ng/mL at Day 168.

Secondary efficacy endpoints included determination of serum LH, FSH and PSA concentrations. By Day 14 after the first injection, mean LH and FSH serum levels had decreased below baseline concentrations, showing the response of the prostate cancer to androgen ablation. Concentrations remained well below baseline values from Day 28 until the end of the study. During treatment, median PSA serum levels gradually decreased (first month) and remained below baseline level until the end of study. PSA concentrations also showed high variability among patients throughout this study.

The leuprolide PK profile obtained in a sub-group analysis (N=30) confirmed the sustained release pattern of ZEULIDE DEPOT 22.5 mg for the duration of the study.

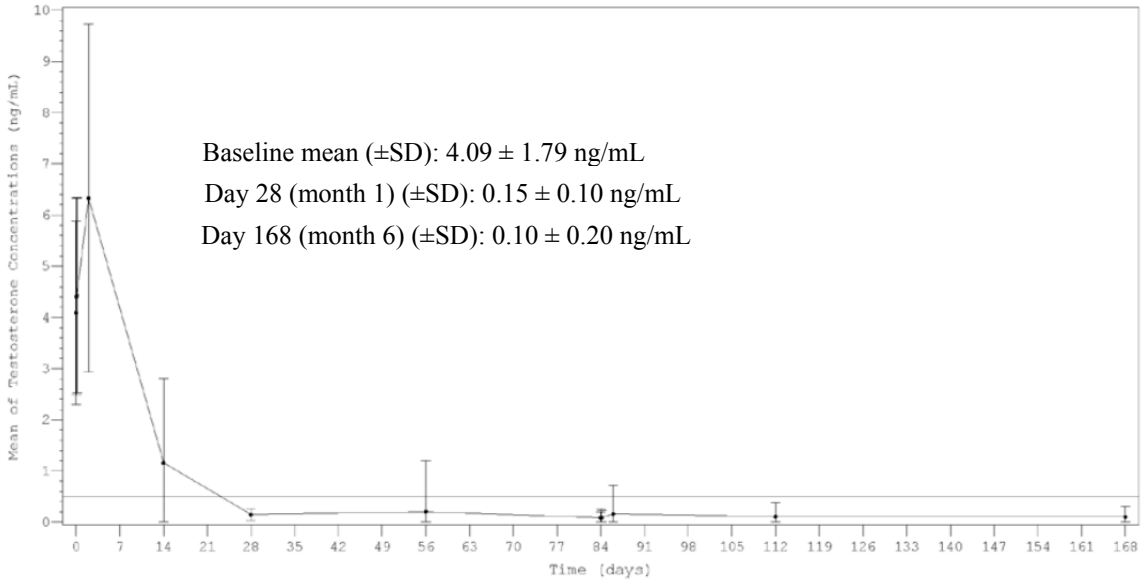


Figure 2: Plasma Testosterone Concentrations (Mean ± SD) for Patients (N=161) Who Received 2 Monthly i.m. Injections of ZEULIDE DEPOT 22.5 mg

An assessment of WHO/ECOG performance status showed stability in most patients with >76% (1-Month) and >82% (3-Month) having a performance status of 0 throughout the study, indicating that they were fully active and able to carry on all pre-disease performances without restriction. All summaries of bone pain, urinary symptoms, and urinary pain indicated good symptom control and were constant throughout each study, with no evidence of flare responses.

The observed safety profile of ZEULIDE DEPOT 3.75 mg (1-Month) and 22.5 mg (3-Month) was similar to that of other products containing leuprolide acetate.

DETAILED PHARMACOLOGY

Leuprolide acetate is an analog of luteinizing hormone-releasing hormone. Following the administration of leuprolide acetate, there is an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). This causes a transient increase in levels of gonadal steroids (testosterone and dihydrotestosterone in males, and oestrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate at therapeutic doses inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. As a result, testosterone is reduced in males to levels associated with castration (≤ 0.5 ng/mL in serum), and oestrogen in females is reduced to postmenopausal levels. These decreases are observed within two to four weeks after the start of treatment, and the effects are reversible upon discontinuation of drug therapy.

Animal Pharmacology

The pharmacological activity of ZEULIDE DEPOT 3.75 mg was evaluated in Beagle dogs. In general, castrate levels were achieved by Day 7 or 14 and testosterone levels remained below castration levels for the remainder of the sampling periods, with good evidence of efficacy being maintained up to Day 42 after a single i.m. administration.

TOXICOLOGY

Acute Toxicity

Published studies on a sustained release formulation of leuprolide acetate demonstrated that the product has a low order of acute toxicity in mice and rats, with LD_{50}'s above 5000 mg/kg (greater than 400 mg/kg of leuprolide acetate) for oral, subcutaneous and intraperitoneal routes of administration, and above 2000 mg/kg (greater than 160 mg/kg as leuprolide acetate) for intramuscular injection. The only clinical signs observed were related to local effects at the site of injection.

Long-term Toxicity

Rat

Leuprolide acetate for depot suspension was administered intramuscularly to three groups of male rats at doses from 10, 30 and 100 mg/kg/week (corresponding to 0.8, 2.4 and 8.0 mg/kg/week of leuprolide acetate injection) once a week for 13 weeks. Rats dosed at 100 mg/kg/week showed atrophy of testes; in addition, white spots were noted at the injection sites. The atrophy of the testes was reported to be due to the hormonal action of leuprolide acetate injection; the "no-toxic-effect" dose was considered to be 100 mg/kg/week.

In another toxicity study, male rats were given leuprolide acetate for depot suspension subcutaneously once a week for 3 weeks, at doses of 30 mg/kg/week (corresponding to 2.4 mg/kg/week of leuprolide acetate injection). Atrophy of the testes, and a slight induration were noted. The "no-toxic effect" dose was considered to be 30 mg/kg/week.

In a third study, leuprolide acetate for depot suspension was given subcutaneously to groups of male and female rats, at doses of 0, 10, 30 and 100 mg/kg/week once a week for 13 weeks (corresponding to 0, 0.8, 2.4 and 8 mg/kg/week of leuprolide acetate injection). Atrophy of the testes was noted, with induration at injection site; in female rats, the vagina failed to open throughout the dosing period. Leuprolide acetate for depot suspension produced changes related to the expected pharmacologic effects. The "no-toxic-effect" dose was considered to be 100 mg/kg/week.

Dog

In two different studies, female and male beagle dogs were given leuprolide acetate for depot suspension subcutaneously for 13 weeks, once a week at doses of 10, 30, 100 mg/kg/week, corresponding to 0.8, 2.4 and 8 mg/kg/week leuprolide acetate injection. No death was reported.

Signs and symptoms include inflammatory lesions at the injection sites, and atrophic changes of the primary and accessory sex glands. The injection site change, seen in both control and test groups, was induced by the microcapsule, not leuprolide, and was reversible.

Special Studies

To investigate the effect of leuprolide acetate at the site of injection, the local toxicity of formulations very similar to ZEULIDE DEPOT 3.75 mg was evaluated in different animal models.

Rat and Dog
Histopathology in rats and dogs were examined after subcutaneous administration of either the sustained-release form of leuprolide acetate (leuprolide acetate micro capsulated in PLGA) or the PLGA placebo. Animals were treated for 13 weeks (rats and dogs) and 12 months (rats). Histopathogical evaluation of the injection site only identified granulation tissues accompanied by cyst that disappeared within 10 or 13 weeks of the administration, respectively. These changes were characterized mainly by foreign body reactions caused by the PLGA.

Rabbit
Local tolerance of the sustained-release formulation with and without the inclusion of the leuprolide acetate (a total of four subcutaneous injections were given once every 4 weeks) has been investigated in rabbits. Macroscopic and microscopic examinations (Days 2, 14 and 56 after the last injection) yielded similar observations were made for formulations with and without leuprolide acetate. A reaction to the foreign body, in the absence of toxicological changes in the surrounding skin and muscle tissue suggest an irritant potential for these formulations as very low.

Guinea Pig
Two studies were performed to evaluate the potential of leuprolide acetate for depot suspension to produce either systemic anaphylaxis or delayed hypersensitivity reactions in guinea pigs.

Preliminary antigenicity study. Leuprolide acetate for depot suspension was given to guinea pigs at a dose of 123 mg/kg every 2 weeks by intramuscular route 4 times, and once by subcutaneous route 2 weeks after the last intramuscular dose. Results were compared to controls treated with placebo-microcapsule 122 mg/kg intraperitoneally, or with ovalbumin 5 mg/animal intravenously. No systemic anaphylactic reactions were observed with animals treated with leuprolide acetate for depot suspension and placebo-microcapsule, but some induced equivocal weak antibody production was noted.

In a second study, the sensitization potential of leuprolide acetate for depot suspension at doses of 50 mg/animal/dosing by intramuscular (systemic anaphylaxis) or at doses of approximately 7.2 mg/animal/dosing (0.05 mL of a 144.23 mg/mL of suspension) intradermal (delayed hypersensitivity), were compared to those seen with gelatin, egg albumin or captan. No signs of anaphylactic reactions nor delayed hypersensitivity were observed for leuprolide acetate for depot suspension, while signs of anaphylactic reactions (such as nose scratching, sneezing, dyspnea or local irritation) were noted with other compounds.

Mutagenicity

A sustained-release formulation of leuprolide was not mutagenic in either an *in vitro* cytogenetic assay using Chinese hamster lung cells or an *in vivo* micronucleus assay in mice. In a bacteria reversed mutation assay (Ames Test) using *E. coli* and *S. typhimurium*, leuprolide acetate was not found to be mutagenic.

Carcinogenicity

Studies to determine the carcinogenic potential of ZEULIDE DEPOT have not been conducted.

Two rodent carcinogenicity studies were conducted for two years with daily doses of 0.6, 1.5 and 4 mg/kg/day of leuprolide acetate in the rat, and with 0.6, 6 and 60 mg/kg/day in the mouse.

In rats, a dose-related incidence of pituitary hyperplasia, hypertrophy and benign pituitary adenomas were noted at 12-month necropsy, while a statistically significant dose-related incidence of benign pituitary adenomas was observed in both male and female rats after 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg).

In mice, no drug-induced neoplastic changes or pituitary abnormalities were observed at doses as high as 60 mg/kg for two years.

Patients have been treated with leuprolide for up to three years with doses as high as 10 mg/day, and for two years with doses as high as 20 mg/day. Clinical signs of pituitary abnormalities have not been observed in any of these patients.

Reproduction and Teratology

Reproduction and teratology studies conducted with a sustained release formulation indicate all effects observed are related to consequences or repeated administration of this pharmacologic agent. Fertility studies, where male rats were dosed once every four weeks for three doses prior to mating, showed that the drug produced reversible atrophy of the testes or accessory sex organs at doses as low as 0.024 mg/kg (as leuprolide), and a decrease in LH, FSH and testosterone levels. A reversible decrease in copulation and implantation sites was also observed at the high dose of 2.4 mg/kg. No effects on the fetuses were observed.

Female rats dosed at 2.4 mg leuprolide acetate/kg once, four weeks prior to mating, caused an interruption in the oestrus cycle and decreased vaginal size. Weights of the ovaries and uterus were decreased. Following mating, corpora lutea and the number of implantation sites were decreased at 0.24 mg/kg and above; the number of live fetuses was reduced at 2.4 mg/kg and above.

No abnormal development was noted in the fetuses. The sustained release formulation of leuprolide was not teratogenic in either rats or rabbits. In the perinatal study, the administration of the sustained release formulation of leuprolide prior to delivery at up to 8 mg/kg showed effects on sex organ weights, but no adverse effects on the fetuses, including weights of their sex organs.

In another study, when administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the 3.75 mg dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities.

REFERENCES

1. Chatani F, Yamamoto KI, Shikata M, Kuzuna S, Miyajima H, Chiba S. Toxicity of TAP-144-SR and TAP-144 after repeated administrations and carcinogenicity of TAP-144 in animals. Jpn Pharmacol Ther. 1990;18 Suppl:575-88.

2. Collinson MP, Tyrell CJ, Hutton C. Osteoporosis occurring in two patients receiving LHRH analogs for carcinoma of the prostate. Calcif Tissue Int. 1994;54:327-8.

3. Fujikawa K, Nakamura M, Kimura Y, Samejima K, Hitotsumachi S. Mutagenicity studies of TAP-144-SR – *In vitro* cytogenetic test. Jpn Pharmacol Ther. 1990;18 Suppl:661-6.

4. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, *et al*. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. Circulation. 2010;121(6):833-40.

5. Maberger M, Kaisary AV, Shore ND, Karlin GS, Savulsky C, Mis R, Leuratti C, Germa JR. Effectiveness, pharmacokinetics, and safety of a new sustained-release leuprolide acetate 3.75-mg depot formulation for testosterone suppression in patients with prostate cancer: a Phase III, open-label, international multicenter study. Clin Ther. 2010 Apr;32(4):744-57.

6. MacLeod TL, Eisen A, Sussman GL. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. Fertil Steril. 1987;43(3):500-2.

7. McGrath SA, Diamond T. Osteoporosis as a complication of orchiectomy in 2 elderly men with prostatic cancer. J Urol. 1995;154:535-6.

8. Mikoda T, Aomori T, Chiba S. Single administration toxicity study of TAP-144-SR in mice and rats. Jpn Pharmacol Ther. 1990;18 Suppl:569-73.

9. Nakamura M, Kimura Y, Nakajima Y, Hitotsumachi S. Mutagenicity study of TAP-144-SR – Micronucleus test in mice. Jpn Pharmacol Ther. 1990;18 Suppl:667-71.

10. Ooshima Y, Yoshida T, Sugitani T, Sudo K, Ihara T. Effect of TAP-144-SR on fertility and general reproductive performance of rats. 1990;18 Suppl:589-607.

11. Sakamoto Y, Nagayabu O, Yamamoto K, Nakamura N, Nakajima Y, Kikuchi Y. Mutagenicity study of TAP-144-SR – Reversion test in bacteria. 1990;18 Suppl:651-60.

PART III: CONSUMER INFORMATION

Pr ZEULIDE DEPOT™
Leuprolide acetate for depot suspension

This leaflet is part III of a three-part "Product Monograph" published when ZEULIDE DEPOT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZEULIDE DEPOT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZEULIDE DEPOT is used in the palliative treatment of advanced prostate cancer and/or prostate cancer that has spread (metastasized) to other parts of the body. Palliative treatment is the relief of symptoms associated with a disease; it is not a cure.

What it does:
ZEULIDE DEPOT is a member of a class of drugs known as luteinizing hormone-releasing hormone analogs, also called LH-RH analogs.

Leuprolide, the active medication inside ZEULIDE DEPOT, works by reducing the amount of testosterone in the body. Testosterone, the male hormone produced naturally by the testicles, is used by prostate cancer cells for their growth. When the body's supply of testosterone is lowered, the mass of cancerous cells usually shrinks or stops growing, which may result in a reduction of symptoms related to the disease.

When it should not be used:
Do not use ZEULIDE DEPOT:
- If you are allergic to leuprolide acetate, any similar LH-RH analogs (e.g., histrelin, desorelin), or any of the non-medicinal ingredients in ZEULIDE DEPOT.
- In women especially, those who are or may become pregnant or who are breastfeeding.
- If you are less than 12 years of age

What the medicinal ingredient is:
Leuprolide acetate

What the non-medicinal ingredients are:
Vial: Mannitol, poly (D, L-lactide-co-glycolide) 50/50 (3.75 mg), polylactic acid (22.5 mg), polysorbate 80, sodium carboxymethylcellulose, and triethyl citrate.
Syringe: Mannitol and water for injection. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

What dosage forms it comes in:

ZEULIDE DEPOT is a lyophilized (freeze-dried) powder for injection. ZEULIDE DEPOT provides 3.75 mg (1-Month), or 22.5 mg (3-Month) leuprolide acetate when prepared by your doctor according to the directions.

ZEULIDE DEPOT is supplied in single dose kits containing one vial of lyophilized leuprolide acetate, one prefilled syringe containing 2 mL of diluent, one adaptor system, and one sterile 21 G needle.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ZEULIDE DEPOT should be prescribed by a doctor experienced with this type of drug.

ZEULIDE DEPOT may cause:
- Worsening of symptoms of prostate cancer at the beginning of the treatment
- Bone thinning (osteoporosis)
- Sudden cardiac death
- Pituitary apoplexy (bleeding in your pituitary gland or blockage of blood flow)
- Drug-induced liver injury (injury to liver caused by medications)

Hormonal therapies for prostate cancer that reduce testosterone levels may lead to side effects such as loss of sexual desire (libido) and impotence (erectile dysfunction). These symptoms have been observed to reverse when treatment is stopped. However, whether the clinical symptoms of induced hypogonadism (inability of the testicle to produce testosterone and/or sperm) will reverse in all patients has not yet been established.

ZEULIDE DEPOT is not indicated for use in women or children less than 12 years of age, as safety and efficacy have not been established in these groups of patients.

BEFORE you use ZEULIDE DEPOT talk to your doctor or pharmacist if you:
- have previous history of obstructive uropathy (difficulty urinating due to a block in the urinary tract)
- have family history of osteoporosis or are a chronic user of drugs that can reduce bone mass such as anticonvulsants, corticosteroids, alcohol and/or tobacco. ZEULIDE DEPOT can cause thinning of the bone and may pose additional risk in patients with such a history.
- have a history of heart disease or disorders, or have a genetic heart condition called "long QT syndrome".
- have high blood sugar (diabetes), ZEULIDE DEPOT may affect your blood sugar and you may need to test your blood sugar more frequently while receiving treatment with ZEULIDE DEPOT.
- have low red blood cell counts; ZEULIDE DEPOT may cause a decrease in red blood cells (anemia).
- have bleeding disorders, thrombocytopenia (low count of cells responsible for clotting) or are taking anticoagulants (blood-thinners).

Driving and using machines: Before you perform tasks, which may require special attention, wait until you know how you

respond to ZEULIDE DEPOT. The ability to drive and use machines may be impaired due to visual disturbances and dizziness.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with ZEULIDE DEPOT include, but are not limited to:

- Antiarrhythmic drugs (used to treat abnormal heart rhythm) such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, flecainide, propafenone, dronedarone;
- Antipsychotic drugs (used to treat mental disorders) such as: chlorpromazine;
- Antidepressant drugs (used to treat depression) such as: amitriptyline, nortriptyline;
- Morphine-like medicines (e.g., methadone);
- Antibiotics such as erythromycin, clarithromycin, azithromycin, moxifloxacin;
- Antifungals;
- Antimalarials, such as quinine;
- Medicines used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery such as ondansetron;
- Medicines used for the relief of bronchospasm (tightening of the muscles that line the airways (bronchi) in your lungs) in conditions like asthma and chronic obstructive pulmonary disease such as salbutamol.

PROPER USE OF THIS MEDICATION

Usual dose:

ZEULIDE DEPOT is given as an injection into a muscle by your doctor in either of two dosage forms: 3.75 mg once monthly or 22.5 mg once every three months.

It is very important that your doctor check your progress at regular medical visits. Your doctor will perform physical exams, check your blood and order any other tests (CT scan, X-rays, ECG, etc.) as needed during these visits. Your doctor, or health care provider, will administer ZEULIDE DEPOT for you during your scheduled visits.

If you need more information, ask your doctor.

Administration

The vial of ZEULIDE DEPOT should be reconstituted with the ready to use diluent provided in the syringe immediately prior to administration of vial contents by intramuscular injection. Make sure an aseptic technique is followed.

No other diluent can be used for reconstitution of ZEULIDE DEPOT.

The product must be brought to room temperature before administration. Some product may cake or clump at the vial wall. This is considered normal. The product is meant for a single injection. Any remaining solution must be discarded.

Reconstitute ZEULIDE DEPOT according to the following instructions:

Remove (i) the blue cap from the vial, (ii) the grey cap from the syringe barrel and then (iii) the blister pack from the vial adapter (Step 1)

Attach the adapter system to the vial until a "clicking" sound is heard (Steps 2 and 3).

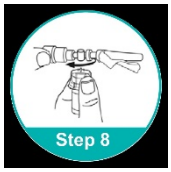
Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter (Step 4). Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

While keeping the syringe and vial securely coupled in an upright position, slowly push the plunger in order to transfer all the diluent into the vial (Step 5).

With the syringe still coupled to the vial, shake the vial gently for approximately one minute until a uniform milky-white suspension is obtained (Step 6).

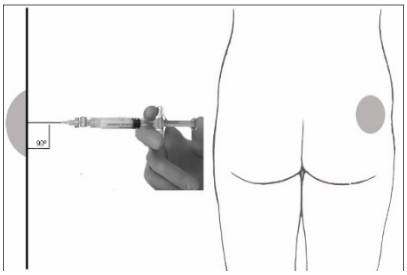
Turn the system upside down, and carefully pull out the plunger to absorb the resuspended drug contained within the vial (Step 7).

Detach the syringe from the adaptor system by twisting the upper piece of the adaptor counter-clockwise (Step 8). The drug is ready to be used.



Lift up the safety cover (Step 9) and remove the clear plastic needle shield by pulling it from the assembly (Step 10). The safety cover should be perpendicular to the needle, with the needle facing away from you.

Clean the injection area with an alcohol swab and let the skin dry. Inject the suspension intramuscularly into the upper outer quadrant of the gluteus.



NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock. If blood is present, remove the needle immediately. Do not inject the medication.

After injecting the product, immediately activate the safety mechanism by centering your thumb or forefingers on the textured finger pad area of the safety cover and pushing it forward over the needle until you hear or feel it locked (Step 11).

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is very important that you keep all scheduled appointments with your doctor. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of ZEULIDE DEPOT injections is an important part of treatment.

Maintaining testosterone suppression is a key element in treating the symptoms of hormone-dependent prostate cancer.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In the first few weeks of taking ZEULIDE DEPOT, your testosterone levels will initially increase and then decline over several weeks. During this period some patients may experience worsening of urinary symptoms (difficulty urinating, blood in the urine) and/or a temporary increase in bone pain. Should this occur, contact your doctor immediately.

The following side effects are commonly experienced after the first dose and occur due to decreasing levels of testosterone in the body:

- general pain or flu-like symptoms
- hot flashes/sweats
- decreased libido
- joint and muscle pain
- emotional changes such as feeling depressed
- worsening urinary symptoms

Other side effects include:

- feeling tired, weakness
- increased appetite
- headache

Should these side effects persist or if they are severe, contact your doctor immediately.

A local skin reaction may occur: pain, irritation, discomfort, redness, bruising, and/or swelling at the injection site. These reactions usually are mild and disappear after a few days. If they persist or worsen, tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or		Stop taking drug and seek immediate medical help
		Only if sever	In all case	
Very Common	Hot flashes		✓	
Common	Erectile dysfunction		✓	
	Heavy sweating, cold sweats, night sweats		✓	
	Skin reactions including reaction at site of injection	✓		
Uncommon	Back pain		✓	
	Bone pain		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or		Stop taking drug and seek immediate medical help
		Only if sever	In all case	
	Light-headedness or dizziness		✓	
	Numbness of limbs		✓	
	Persistent nausea or vomiting		✓	
	Trouble urinating (inability to urinate, blood in urine)		✓	
Unknown frequency	**Allergic reaction:** Chest tightness, difficulty breathing, chest pain			✓
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Myocardial Infarction (heart attack): crushing chest pain, shortness of breath, sweating, nausea, pain in the jaw, neck and/or arm			✓
	Pituitary Apoplexy: sudden headache, vomiting, visual changes,			✓
	Seizures or fits			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or		Stop taking drug and seek immediate medical help
		Only if sever	In all case	
	Weakness, numbness, tingling and/or pain in the hands or feet		✓	

This is not a complete list of side effects. For any unexpected effects while taking ZEULIDE DEPOT, contact your doctor or pharmacist.

HOW TO STORE IT

ZEULIDE DEPOT must be kept below 25°C in the original package in order to protect from light. Protect from freezing.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to
Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, PENDOPHARM, Division of Pharmascience Inc., at: 1-888-550-6060.

This leaflet was prepared by PENDOPHARM, Division of Pharmascience Inc., Montreal, QC, H4P 2T4.

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Last revised:
August 14, 2018