

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrZEULIDE DEPOT™

Leuprolide acetate for depot suspension
Lyophilized powder for injection (suspension after reconstitution with diluent),
3.75 mg [1-Month] and 22.5 mg [3-Month]
For intramuscular injection

Luteinizing Hormone-Releasing Hormone (LH-RH) Analog

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RECENT MAJOR LABEL CHANGES

| | |
|----------------------------------------------|---------|
| Use of new PM Template dated September, 2020 | 01/2021 |
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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (< 12 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 14 [CLINICAL TRIALS](#)).

2 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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.
-

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 7 [WARNINGS AND PRECAUTIONS, General](#)).
- Osteoporosis (See 7 [WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Changes in bone Density](#)).
- Sudden cardiac deaths (See 7 [WARNINGS AND PRECAUTIONS, Cardiovascular](#)).
- Pituitary Apoplexy (See 8.5 [POST-MARKET ADVERSE DRUG REACTIONS](#)).
- Drug-induced Liver Injury (See 7 [WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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.

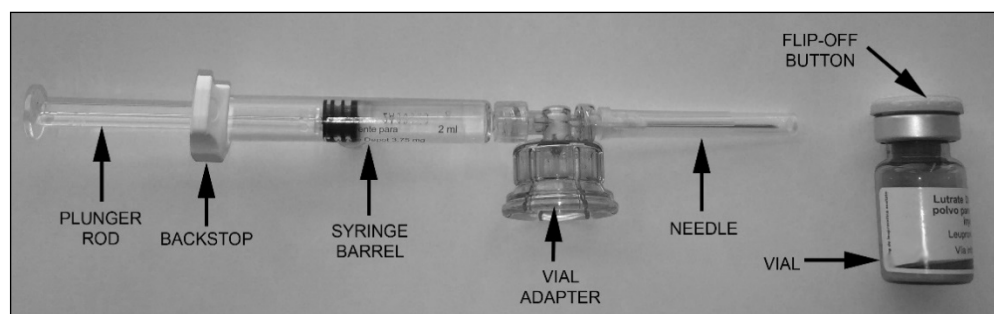
ZEULIDE DEPOT 22.5 mg (3-Month)

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.

4.3 Reconstitution

Table 1 – Reconstitution

| Product | Vial Size | Volume of Diluent to be Added to Vial | Approximate Available Volume | Concentration per mL |
|-----------------|-------------|---------------------------------------|------------------------------|----------------------|
| Zeulide 3.75 mg | 6R (10 mL)* | 2 mL | 1.5 mL | 2.53 mg/ mL |
| Zeulide 22.5 mg | 6R (10 mL)* | 2 mL | 1.6 mL | 14.06 mg/ mL |



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.

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).



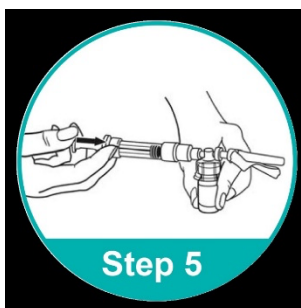
Attach the adapter system to the vial until a “clicking” sound is heard (Steps 2 and 3).



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.



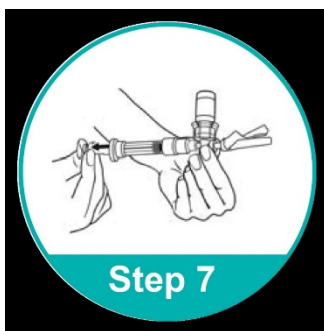
While keeping the syringe and vial securely coupled in an upright position, slowly push the plunger in order to transfer all the diluent into the vial (Step 5).



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).



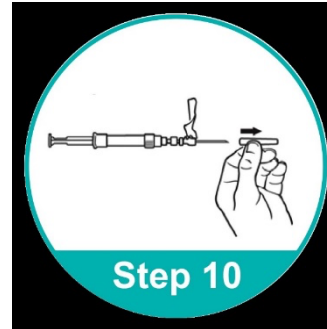
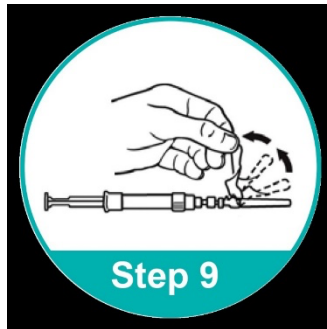
Turn the system upside down, and carefully pull out the plunger to absorb the resuspended drug contained within the vial (Step 7).



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.



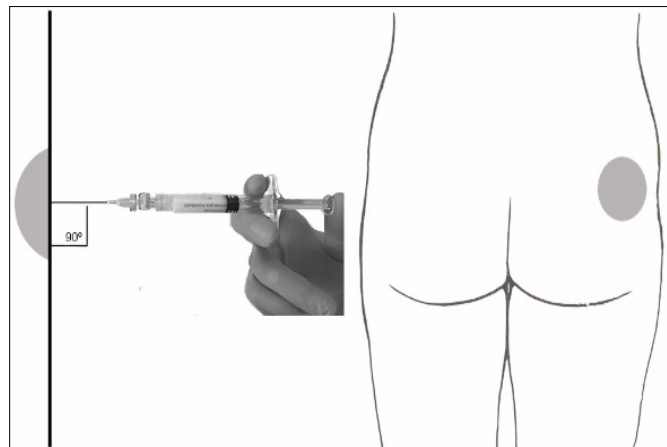
Lift up the safety cover (Step 9) and remove the clear plastic needle shield by pulling it from the assembly (Step 10). The safety cover should be perpendicular to the needle, with the needle facing away from you.



4.4 Administration

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. 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, as shown below.



4.5 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.

5 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.

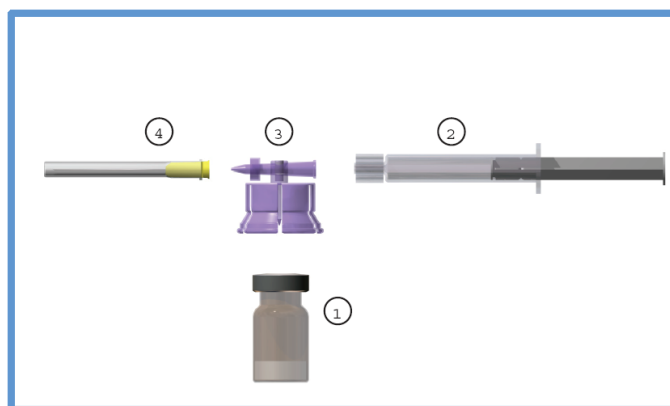
For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intramuscular Injection | <p>Lyophilized powder for injection (suspension after reconstitution with diluent)</p> <p>3.75 mg [1-Month] (5.06 mg/vial to deliver 3.75 mg leuprolide acetate (35% overfill))</p> <p>22.5 mg [3-Month] (28.13 mg/vial to deliver 22.5 mg leuprolide acetate (25% overfill))</p> | <p>3.75 mg [1-Month]: Mannitol, poly (D, L-lactide-co-glycolide; PLGA 50/50), polysorbate 80, sodium carboxymethylcellulose and triethyl citrate</p> <p>22.5 mg [3-Month]: Mannitol, polylactic acid, polysorbate 80, sodium carboxymethylcellulose and triethyl citrate</p> |

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.



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).

7 WARNINGS AND PRECAUTIONS

Please see 3 [SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

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. For more information see 16 [NON-CLINICAL TOXICOLOGY](#).

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 reported 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 9.2 [Drug-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.

Driving and Operating Machinery

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

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.

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 [Endocrine and Metabolism; Reduction in Glucose Tolerance](#) above).

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.

Reproductive Health: Female and Male Potential

- **Function**

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

- **Teratogenic Risk**

ZEULIDE DEPOT is contraindicated in pregnant and nursing women (see 2 [CONTRAINDICATIONS](#); 7.1.1 [Pregnant Women](#)).

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.

7.1 Special Populations

7.1.1 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 (see 2 [CONTRAINDICATIONS](#)).

7.1.2 Breast-feeding

ZEULIDE DEPOT is contraindicated (see 2 [CONTRAINDICATIONS](#)) in nursing women as safety and effectiveness have not been established in this group of patients.

7.1.3 Pediatrics

Pediatrics (<12 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse 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 7 [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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following possibly or probably related systemic adverse reactions were reported by $\geq 2\%$ 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 3).

Table 3: 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%).

8.3 Less Common Clinical Trial Adverse Reactions

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)

| | |
|--------------------------------------------------------------|----------------------------------------------------------|
| <i>Ear and labyrinth disorders:</i> | Vertigo |
| <i>Gastrointestinal disorders:</i> | Abdominal pain lower, diarrhea, nausea, vomiting |
| <i>General disorders and administration site conditions:</i> | Asthenia, feeling hot and cold, feeling jittery, pyrexia |
| <i>Hepatobiliary disorders:</i> | Hyperbilirubinemia |
| <i>Investigations</i> | Alanine aminotransferase increased, aspartate |

| | |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------|
| | aminotransferase increased, body temperature increased, gamma-glutamyltransferase increased |
| <i>Metabolism and nutrition disorders:</i> | Anorexia, hypercholesterolemia, hyperlipidemia, increased appetite |
| <i>Musculoskeletal and connective tissue disorders:</i> | Arthralgia, back pain, muscle spasms, pain in extremity |
| <i>Nervous system disorders:</i> | Somnolence |
| <i>Psychiatric disorders:</i> | Insomnia, libido decreased*, mood altered, sleep disorder |
| <i>Renal and urinary disorders:</i> | Pollakiuria, urinary incontinence, urinary retention |
| <i>Reproductive and breast disorders:</i> | Breast swelling*, breast tenderness, ejaculation failure*, erectile dysfunction* |
| <i>Skin and subcutaneous tissue disorders:</i> | Cold sweat*, periorbital edema, pruritus, urticaria |

* Expected pharmacological consequences of testosterone suppression

ZEULIDE DEPOT 22.5 mg (3-Month)

| | |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Ear and labyrinth disorders:</i> | Tinnitus |
| <i>Eye disorders:</i> | Vision blurred |
| <i>Gastrointestinal disorders:</i> | Abdominal pain upper, constipation, diarrhea |
| <i>General disorders and administration site conditions:</i> | Adverse drug reaction, cold sweat, feeling hot, hyperhidrosis, injection site discomfort/hemorrhage/urticaria/warmth, pain, vessel puncture site pain |
| <i>Investigations</i> | 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 |
| <i>Metabolism and nutrition disorders:</i> | Decreased appetite, hypercholesterolemia |
| <i>Musculoskeletal and connective tissue disorders:</i> | Arthralgia, back pain, musculoskeletal pain, neck pain |
| <i>Nervous system disorders:</i> | Dizziness, dysgeusia, formication, headache, lethargy |
| <i>Psychiatric disorders:</i> | Anger, anxiety, depression, emotional disorder, libido |

| | |
|--------------------------------------------------------|------------------------------------------------------------------------------------------|
| | decreased, sleep disorder |
| <i>Renal and urinary disorders</i> | Nocturia, urinary tract pain, urine flow decreased |
| <i>Reproductive system and breast disorders:</i> | Erectile dysfunction*, nipple pain, pelvic pain, testicular atrophy, testicular disorder |
| <i>Respiratory, thoracic and mediastinal disorders</i> | Pleurisy |
| <i>Skin and subcutaneous tissue disorders:</i> | Cold sweat*, night sweats, papule, pruritus, pruritus generalised, rash |
| <i>Vascular disorder</i> | Flushing |

* Expected pharmacological consequences of testosterone suppression

ECOG: Eastern Cooperative Oncology Group

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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 $\geq 2\%$ 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 8.3 [Less Common Clinical Trial Adverse Drug Reactions](#), Investigations).

8.5 Post-Market Adverse 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.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

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

9.2 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).

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test 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.

10 CLINICAL PHARMACOLOGY

10.1 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 of leuprolide acetate at therapeutic doses inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. This results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels (≤ 0.5 ng/mL). 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.

10.2 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).

10.3 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 (\pm SD) $46.79 (\pm 18.0)$ ng/mL and $48.30 (\pm 18.6)$ 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.

Elimination

No drug excretion study was conducted with ZEULIDE DEPOT.

Special Populations and Conditions

- **Sex.**
- **Pregnancy and Breast-feeding**
- **Genetic Polymorphism** The effect of genetic polymorphism on the pharmacokinetics of ZEULIDE DEPOT was not studied.
- **Hepatic Insufficiency** The pharmacokinetics of the drug in hepatic impaired patients has not been determined.
- **Renal Insufficiency** The pharmacokinetics of the drug in renal impaired patients has not been determined.

11 STORAGE, STABILITY AND DISPOSAL

ZEULIDE DEPOT must be stored below 25°C. Protect from freezing.

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

12 SPECIAL HANDLING INSTRUCTIONS

Allow the product to reach room temperature before using.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

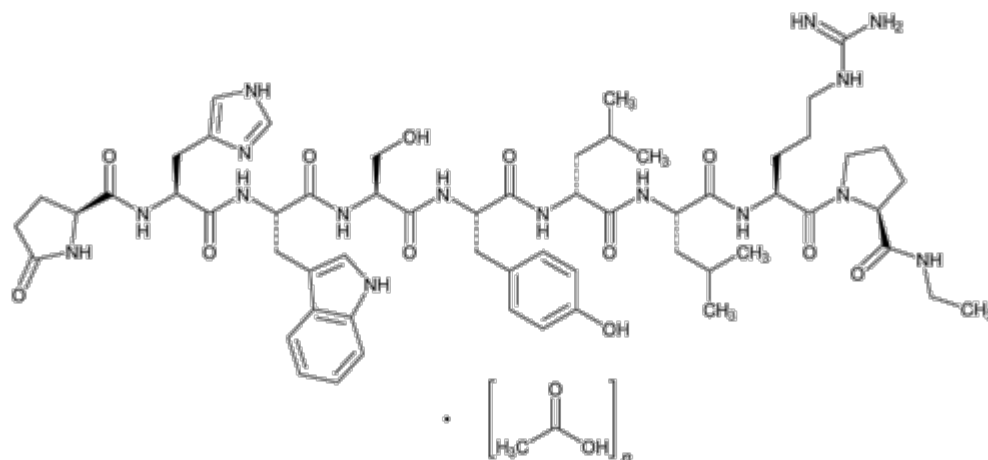
Drug Substance

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 and molecular mass: $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$; 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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials in prostate cancer patients

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------|----------------------------------------------------------------------------|-------|
| ZEULIDE DEPOT 3.75 mg | Open-label, multicentre study conducted to evaluate the safety and efficacy of ZEULIDE DEPOT in prostate cancer patients | 3.75 mg Intramuscularly once every four weeks for 24 weeks | 160 | <u>Mean \pm SD</u> 71.6 \pm 9.2 <u>Range</u> 48-90 | Males |

| | | | | | |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----|---------------------------------------------------------|-------|
| ZEULIDE DEPOT 22.5 mg | Open-label, multicentre study conducted to evaluate the safety and efficacy of ZEULIDE DEPOT in prostate cancer patients | 22.5 mg Multiple dose study to evaluate 2 sequential doses administered in a 3 month interval | 163 | <u>Mean ± SD</u> 71.0 ± 9.0 <u>Range</u> 47-91 | Males |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----|---------------------------------------------------------|-------|

Further details describing the demographics of the study population can be found in the table below.

| 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 |

14.2 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.

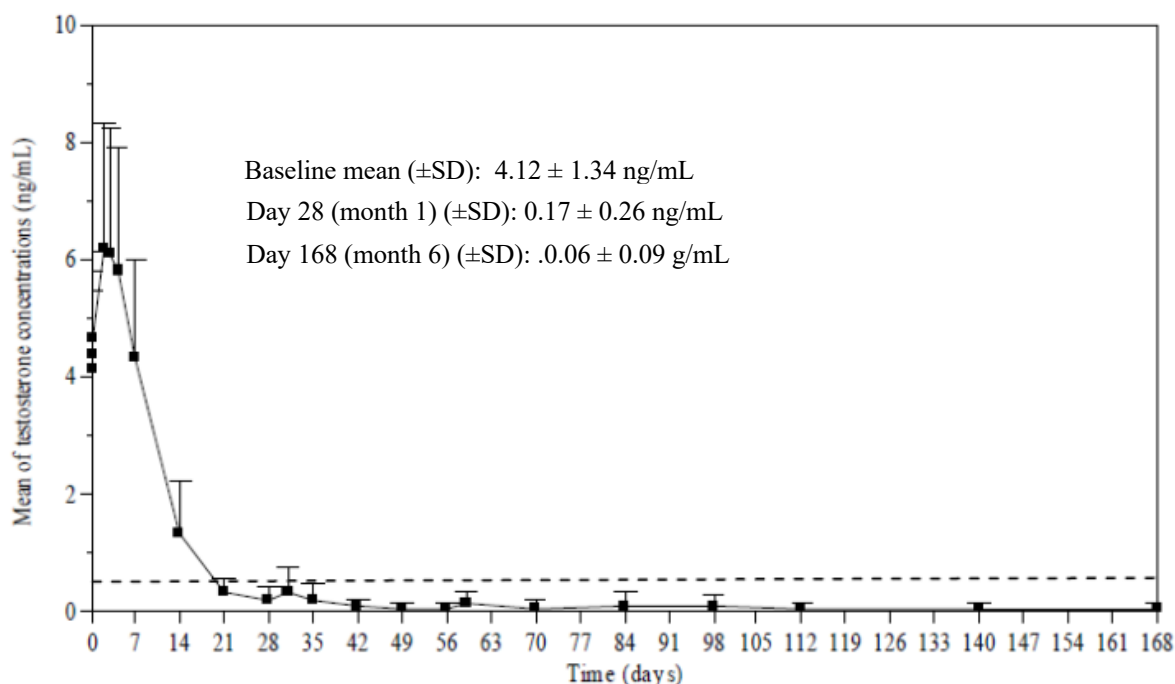


Figure 1: Plasma Testosterone Concentrations (Mean \pm SD) for All Patients (N=160) Who Received 6 Monthly i.m. Injections of ZEULIDE DEPOT 3.75 mg

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.

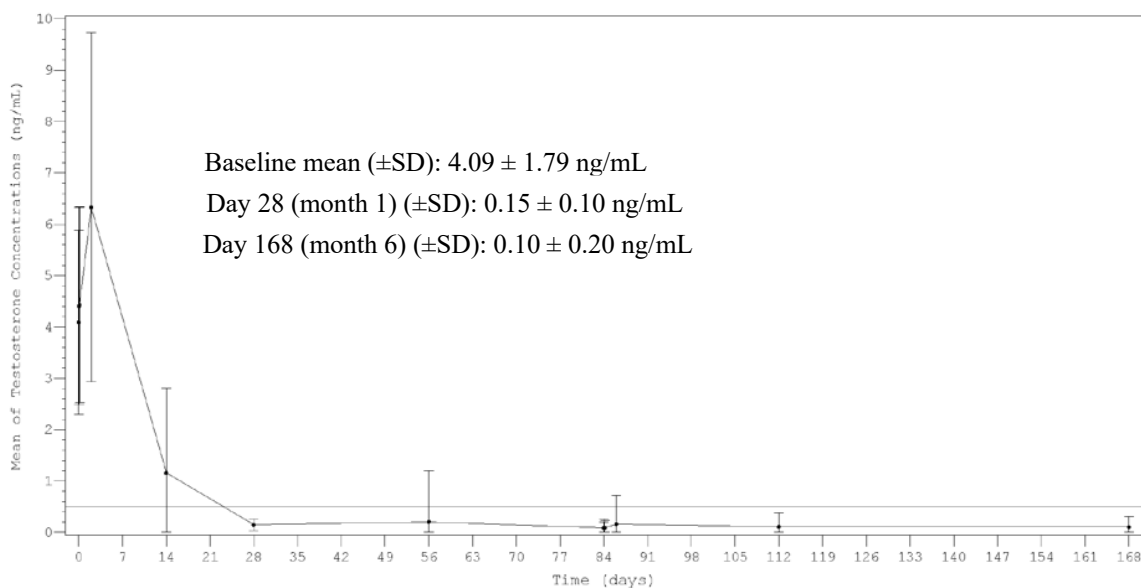


Figure 2: Plasma Testosterone Concentrations (Mean \pm SD) for Patients (N=161) Who Received 2 Monthly i.m. Injections of ZEULIDE DEPOT 22.5 mg

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.

Table 5 - Results of ZEULIDE DEPOT studies in prostate cancer patients

| Primary Endpoints | Associated value and statistical significance for Drug at specific dosages | Associated value and statistical significance for Placebo or active control |
|-------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
|-------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------|

| | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| ZEULIDE DEPOT 3.75 mg injected intramuscularly once every four weeks for 24 weeks will reduce testosterone to, and maintain it at castrate levels (≤ 0.5 ng/mL) in previously untreated prostate cancer patients | <p>By Day 21: 78.7% of patients had achieved medical castration.</p> <p>By Day 28: 96.8% of the patients had achieved castrate levels; 73.1% had achieved levels of ≤ 0.2 ng/mL.</p> <p>No breakthroughs reported throughout the study.</p> <p>At study completion, 92.8% of the patients had testosterone levels ≤ 0.2 ng/mL.</p> | Not applicable |
| Multiple-dose study to evaluate two sequential doses of ZEULIDE DEPOT 22.5 mg administered in a 3-month interval to patients with histologically proven carcinoma of the prostate. | <p>By Day 28: 98.7% of patients had testosterone levels below the castrate threshold (≤ 0.5 ng/mL).</p> <p>By Day 28: 78.0% of the patients had testosterone levels ≤ 0.2 ng/mL.</p> <p>At study completion (Day 168), 99.3% patients maintained castrate levels and 90.7% of the patients presented testosterone levels ≤ 0.2 ng/mL.</p> | Not applicable |

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 LD₅₀'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.

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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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.

Special Toxicology: 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). Histopathological 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^omg/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.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **ZEULIDE DEPOT™**

Leuprolide acetate for depot suspension

Read this carefully before you start taking **ZEULIDE DEPOT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZEULIDE DEPOT**.

Serious Warnings and Precautions

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

ZEULIDE DEPOT may cause:

- Worsening of symptoms of prostate cancer at the beginning of the treatment. Higher levels of testosterone can occur during the first week of treatment with ZEULIDE DEPOT. This can cause:
 - Numbness, tingling, weakness or pain in your bones or limbs.
 - bloody urine or blockage in your urinary tract.
 - Pressure on your spinal cord.
 - Kidney problems.
- **Osteoporosis** (bone thinning) and bone fractures can happen while taking ZEULIDE DEPOT. Your healthcare professional will determine if the benefits outweigh the risks.
- **Sudden heart related deaths.** This includes **heart failure, myocardial infarction** (heart attack), stroke, and QT interval prolongation (causes irregular heart rate). Your healthcare professional will determine if the benefits outweigh the risks.
- **Pituitary apoplexy** (bleeding in, or blockage of blood flow to your pituitary gland). This might happen within 2 weeks of the first dose and some within the first hour.
- **Liver injury** caused by drugs. Liver injury and jaundice (yellowing of skin or white of eyes) can happen while taking ZEULIDE DEPOT.

What is ZEULIDE DEPOT used for?

ZEULIDE DEPOT is used to relieve symptoms of prostate cancer that is advanced (cannot be cured) and/or has spread to other parts of the body. The treatment is called palliative because it cannot cure prostate cancer.

How does ZEULIDE DEPOT work?

ZEULIDE DEPOT belongs to a class of drugs called luteinizing hormone-releasing hormone (LH-RH) analogs.

ZEULIDE DEPOT works by lowering the levels of sex-hormones, like testosterone, in the body. This might help relieve some symptoms related to prostate cancer.

What are the ingredients in ZEULIDE DEPOT?

Medicinal ingredients: Leuprolide acetate

Non-medicinal ingredients:

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.

ZEULIDE DEPOT comes in the following dosage forms:

- Lyophilized (freeze-dried) powder for injection, 3.75 mg (1-Month) or 22.5 mg (3-Month) leuprolide acetate.
- 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.

Do not use ZEULIDE DEPOT if:

- If you are allergic to leuprolide acetate, any similar LH-RH analogs (e.g., histrelin, desorelin), or any other ingredients in ZEULIDE DEPOT.
- You are a woman, especially if you are or may become. ZEULIDE DEPOT might harm your unborn baby.
- You are a woman that is breastfeeding.
- If you are less than 12 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZEULIDE DEPOT. Talk about any health conditions or problems you may have, including if you:

- Have or had urinary tract problems, like a blockage in your urinary tract.
- Have family history of bone problems or are a long-term user of drugs that can lower bone mass such as anticonvulsants (for seizures), corticosteroids (lowers inflammation), alcohol and/or tobacco.
- Have or had heart problems, including a condition called “Long QT syndrome”.
- Have high blood sugar (diabetes).
- Have bleeding disorders, low red blood cell counts (anemia) or low blood platelet counts (thrombocytopenia)
- Are taking anticoagulants (blood-thinner drugs) or antiarrhythmics (heart rhythm drugs).
- Have or had liver and/or kidney problems.
- Have or had depression.

Other warnings you should know about:

ZEULIDE DEPOT can cause serious side effects, including:

- **Convulsions** (muscle spasms or seizures).
- **Behavior and mental status changes:** Depression, mood swings and suicide can happen while taking ZEULIDE DEPOT. Your healthcare professional will talk to you about these mental status problems.
- **Lung and breathing problems:** Chest pain and tightness, coughing up blood, wheezing, strep throat and cold like symptoms can happen while taking ZEULIDE DEPOT.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Diabetes (high blood sugar):

- There is a higher risk of developing diabetes during treatment with Zeulide Depot.

- Your blood sugar should be monitored during treatment. More frequent monitoring may be needed if you are diabetic.

Anemia (low red blood cell count):

- There is a risk of having low red blood cell counts during treatment with Zeulide Depot.
- Your healthcare professional will determine if the benefits outweigh the risks.

Sexual Health and Fertility:

- Hypogonadism (when your body makes little to no sex hormones) can happen while taking ZEULIDE DEPOT. This can lead to sexual/erectile dysfunction and lower sex drive.

Monitoring and Laboratory Tests:

- You will need blood tests before you start ZEULIDE DEPOT and during your treatment. This will help your healthcare professional know how ZEULIDE DEPOT is affecting your blood, blood sugar levels, hormones and other parts of your body (heart, liver and kidneys).
- You may also get an electrocardiogram (ECG) to see how ZEULIDE DEPOT is affecting your heart rhythm.
- X-rays, ultrasounds and CT scans might be needed to see how ZEULIDE DEPOT is affecting your bone and urinary tract health.

Women and Children:

- ZEULIDE DEPOT is not for use in women or children less than 12 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZEULIDE DEPOT:

- Medicines that affect your heart rhythm (antiarrhythmic drugs) such as quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, flecainide, propafenone, dronedarone;
- Medicines used to treat mental problems (antipsychotic drugs) such as chlorpromazine;
- Medicines used to treat depression (antidepressant drugs) such as amitriptyline, nortriptyline;
- Narcotic medicines used to treat pain such as methadone;
- Medicines used to treat bacterial infections such as erythromycin, clarithromycin, azithromycin, moxifloxacin;
- Medicines used to treat fungal infections (antifungals);
- Medicines used to treat malaria (antimalarials) such as quinine;
- Medicines used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery such as ondansetron;
- Medicines used to treat breathing problems, like asthma, such as salbutamol.

How to take ZEULIDE DEPOT:

ZEULIDE DEPOT is given to you by a healthcare professional in a healthcare setting.

Usual Dose:

- 3.75 mg: One injection, once a month.
- 22.5 mg: One injection, once every 3 months.

Overdose:

If you think you, or a person you are caring for, have taken too much ZEULIDE DEPOT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of ZEULIDE DEPOT, contact your healthcare professional as soon as possible.
- It is very important that you follow all planned doses of ZEULIDE DEPOT with your healthcare professional.

What are possible side effects from using ZEULIDE DEPOT?

These are not all the possible side effects you may have when taking ZEULIDE DEPOT. If you experience any side effects not listed here, tell your healthcare professional.

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.

- general pain, cold or flu-like symptoms
- sore throat
- swelling around the eyes, joint, muscle, pelvic, neck, nipple pain
- feeling tired, weakness
- increased appetite
- loss of taste
- headache
- blurry vision
- trouble sleeping
- diarrhea
- constipation
- stomach pain
- feeling hot or cold
- feeling jittery

| Serious side effects and what to do about them | | | |
|---------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| VERY COMMON | | | |
| Hot flashes | | ✓ | |
| COMMON | | | |
| Anorexia (eating disorder): | | ✓ | |
| Behavior and mental status changes: agitation including aggressive behavior | | ✓ | |

| Serious side effects and what to do about them | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| or hostility, depression, emotional and sleep problems | | | |
| Bone pain | | ✓ | |
| Hypogonadism (when your body makes little to no sex hormones): Erectile dysfunction, ejaculation failure, breast swelling/tenderness, low sex drive, testicle problems | | ✓ | |
| Heavy sweating, cold sweats, night sweats | | ✓ | |
| Injection Site Reactions: blistering, itching, pain, hives, redness, bruising, hardened skin, skin damage, tenderness, skin bleeding, warmth in the area around the injection | ✓ | | |
| Lung and breathing problems including pleural effusion (fluid around the lungs): chest pain and tightness, difficult or painful breathing, cough, coughing up blood, wheezing | | ✓ | |
| Tinnitus: ringing, buzzing, clicking or hissing in the ears | ✓ | | |
| Vertigo (Light-headedness or dizziness) | | ✓ | |
| UNCOMMON | | | |
| Back pain | | ✓ | |
| Numbness of limbs | | ✓ | |
| Persistent nausea or vomiting | | ✓ | |
| Urinary tract disorders: difficulty and pain when passing urine, exaggerated sense of needing to urinate, blood in urine, urinary tract pain, less urine | | ✓ | |
| UNKNOWN FREQUENCY | | | |
| Allergic reaction: Chest tightness, difficulty breathing, chest pain, sneezing, coughing | | | ✓ |
| Liver Disorder/Injury: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, fever, fatigue, weakness | | ✓ | |
| Osteoporosis (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking | | ✓ | |
| Heart Failure, Myocardial Infarction (heart attack): crushing chest pain, shortness of breath, sweating, nausea, | | | ✓ |

| Serious side effects and what to do about them | | | |
|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| pain in the jaw, neck and/or arm, irregular heartbeat, fluid retention, swelling in legs, ankles and feet, fluid retention | | | |
| Pituitary Apoplexy (bleeding in, or blockage of blood flow to your pituitary gland): sudden headache, vomiting, visual changes, | | | ✓ |
| Convulsions (seizures, muscle spasms) | | | ✓ |
| Weakness, numbness, tingling and/or pain in the arms, hands, legs or feet | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.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.

Storage:

- ZEULIDE DEPOT must be kept below 25°C. Protect from freezing.
- ZEULIDE DEPOT will be managed and stored by healthcare professionals.
- Keep out of reach and sight of children.

If you want more information about ZEULIDE DEPOT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.veritypharma.com, or by calling 1-800877-4414.

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