Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GENPROLEX INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GENPROLEX INJECTION:

Each 1 mL contains Leuprolide Acetate USP 5,0 mg

Each 1 mL contains Benzyl Alcohol USNF 9,0 mg as a preservative

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Subcutaneous injection

A clear colourless solution, essentially free from visible particles

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GENPROLEX is indicated in the palliative treatment of advanced prostatic cancer.

It offers an alternative treatment of prostatic cancer when orchiectomy or oestrogen administration is either not indicated or unacceptable to the patient.

4.2. Posology and method of administration

Posology

The recommended dose of **GENPROLEX** injection is 1 mg (0,2 mL) administered as a single daily subcutaneous injection.

Method of administration

Information for patients:

Directions for using **GENPROLEX**

a) Wash hands thoroughly with soap and water
b) Remove the plastic cover on the bottle to expose the rubber stopper. Wipe the metal ring and rubber stopper with an alcohol swab each time you use **GENPROLEX**. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE. Exchange it at your pharmacy for another container.
c) Pull the plunger of the syringe back until the plunger tip is at the 0,2 mL (20 unit) mark.
d) Push the needle through the centre of the rubber stopper on the **GENPROLEX** bottle.
e) Push the plunger all the way in to expel air into the bottle.
f) Invert the bottle and syringe. Check to make sure the tip of the needle is in the liquid. Pull the plunger slowly backwards until the syringe fills to the 0,2 mL (20 unit) mark.
g) Ensure that no air bubbles are in the syringe. If air bubbles are present, push the plunger forward to expel air into the bottle and refill the syringe to the 0,2 mL (20 unit) mark.
h) Remove the needle from the bottle. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
i) Wipe the injection site with an alcohol swab.
j) Hold the syringe in one hand. Hold the skin taut or pull up a little skin if needed, with the other hand.

k) Hold the syringe alongside the skin and slide the needle quickly just under the skin as far as it will go at a 90° angle. Inject the drug by pushing the plunger.

l) Hold an alcohol swab on your skin where the needle was inserted and pull the needle at the same angle as it was inserted.

m) To protect you skin, inject each daily dose in a different spot.

n) Use the disposable syringe only once and dispose of it carefully.

As with other medicines administered chronically by subcutaneous injection, the injection site should be varied periodically.

4.3. Contraindications

GENPROLEX is contraindicated in patients hypersensitive to leuprolide acetate or similar nonapeptides or to any of the excipients listed in section 6.1.

GENPROLEX should not be administered to patients who have had anaphylactic reaction to leuprolide acetate (see section 4.4).

Although this formulation is not indicated for use in women, **GENPROLEX** is contraindicated in:

- Women who are or may become pregnant while receiving **GENPROLEX**;
- Women who are breastfeeding;
- Patients with undiagnosed, abnormal vaginal bleeding.

4.4. Special warnings and precautions for use

Initially **GENPROLEX**, causes increases in serum levels of testosterone to approximately 50 % above baseline during first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of **GENPROLEX** treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. Isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

For patients at risk initiation of therapy with daily **GENPROLEX** injection for the first two weeks to facilitate withdrawal of treatment may be considered.

Periodic monitoring of serum testosterone and prostate-specific antigen (PSA) levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that 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.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.
Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycaemia or diabetes.

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Based on findings in animal studies, **GENPROLEX** may cause foetal harm when administered to a pregnant woman. In animal developmental and reproductive toxicology studies, administration of the monthly formulation of **GENPROLEX** on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-foetal toxicity in animals at doses less than the human dose, based on body surface area, using an estimated daily dose. Pregnant patients and females of reproductive potential should not take **GENPROLEX**.

Effect on QT/QTc Interval

QT-prolongation has been observed during long-term androgen deprivation therapy. Medical practitioners should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, congestive heart failure, and in patients taking Class IA (e.g., quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antidysrhythmic medications.

Bone Mineral Density

Bone mineral density changes can occur during any hypoestrogenic state in women and in long-term use in prostate cancer in men. There is no data in men regarding reversibility after

withdrawal of **GENPROLEX**. In women, bone mineral density loss may be reversible after withdrawal of **GENPROLEX** (see section 4.8).

Convulsions

Post-marketing reports of convulsions have been observed in patients on **GENPROLEX** therapy. These include patients in the female and paediatric populations, patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumours, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

Laboratory Tests

Response to **GENPROLEX** should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long medicine as administration continued.

GENPROLEX contains Benzyl alcohol.

Patients with known allergies to benzyl alcohol, an ingredient of the medicine's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk if accumulation toxicity (metabolic acidosis).

4.5. Interaction with other medicines and other forms of interaction

Medicine interactions

Pharmacokinetic-based studies have not been conducted with **GENPROLEX**. However, due to leuprolide acetate being a peptide that is primarily degraded by peptidase and not by cytochrome P·450 enzymes as noted in specific studies, and due to this compound being only 46 % bound to plasma proteins, medicine interactions are not expected to occur.

Medicine/Laboratory Test Interactions

Administration of **GENPROLEX** in women in therapeutic doses results in suppression of the pituitary- gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of **GENPROLEX** may be misleading.

4.6. Fertility, pregnancy and lactation

Pregnancy

GENPROLEX is contraindicated in women who are or may become pregnant while receiving **GENPROLEX**. Before starting treatment with **GENPROLEX** it is advisable to establish whether the patient is pregnant.

Breastfeeding

It is not known whether **GENPROLEX** is excreted in human milk. Therefore **GENPROLEX** should not be administered to breastfeeding mothers.

Fertility

Based on findings in animals and mechanism of action, **GENPROLEX** may impair fertility in males of reproductive potential.

4.7. Effects on ability to drive and use machines

GENPROLEX may have a moderate influence on the ability to drive and use machines. **GENPROLEX** may be associated with hypotension, dizziness and blurred vision. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8. Undesirable effects

a. *Summary of the safety profile*

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of **GENPROLEX**. Therefore, an increase in clinical signs and symptoms may be observed (see section 4.4).

Worsening of pre-existing signs and symptoms during the first weeks of treatment may occur. Worsening of symptoms may contribute to paralysis with or without fatal complications.

b. *Tabulated list of adverse reactions*

The below listed adverse reactions reports on effects commonly associated with the pharmacological actions of **GENPROLEX** on the steroidogenesis and reported clinical and post-marketing adverse events as well as post marketing adverse events experience.

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequency not known- reported post marketing	Infection, urinary tract infection, pharyngitis, Allergic reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	Prostate tumour flare, aggravation of prostate cancer
	Frequency not known- reported post marketing	Skin cancer
Blood and lymphatic system disorders	Frequency not known- reported post marketing	Anaemia.
Immune system disorders	Frequency not known	Anaphylactic reactions
Endocrine disorders	Frequency not known	Goitre, pituitary apoplexy
Metabolism and nutrition disorders	Frequent	Weight gain, weight loss, anorexia
	Frequency not known- reported post marketing	Diabetes mellitus, increased appetite, hypoglycaemia, dehydration, hyperlipidaemia, hyperphosphataemia, hypoproteinaemia

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Psychiatric disorders	Frequent	Loss or decreased libido, increased libido, insomnia
	Frequency not known - reported post marketing	Mood swings, nervousness, libido increased, insomnia, sleep disorder, depression, anxiety, delusion, suicidal ideation, suicide attempt
Nervous system disorders	Frequent	Headache, muscular weakness, dizziness, paraesthesia, lethargy, somnolence, dysgeusia, hypoaesthesia, memory impairment
	Frequency not known- post marketing	Dizziness, headache, paraesthesia, lethargy, memory impairment, dysgeusia, hypoaesthenia, syncope, neuropathy peripheral, cerebrovascular accident, loss of consciousness, transient ischaemic attack, paralysis, neuromyopathy, convulsions
Eye disorders	Frequent	Vision blurred
	Frequency not known – reported	Vision blurred, eye disorder, visual impairment, amblyopia, dry eye

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
	post marketing	
Ear and labyrinth disorders	Frequency not known reported post marketing	Tinnitus, hearing impaired
Cardiac disorders	Frequent	Cardiac failure, congestive dysrhythmia, myocardial infarction,
	Frequency not known- reported post marketing	Cardiac failure, congestive dysrhythmia, myocardial infarction, angina pectoris, tachycardia, bradycardia, sudden cardiac death
Vascular disorders	Frequent	Vasodilation, [~~H~~]hot flushes, hypotension, orthostatic hypotension.
	Frequency not known- reported post marketing experience	Peripheral oedema, Lymphoedema, hypertension, phlebitis, thrombosis, hypotension, varicose vein
	Frequency not known- reported post marketing experience	Pleural rub, pulmonary fibrosis, epistaxis, dyspnoea, haemoptysis, cough, pleural effusion, lung infiltration, respiratory disorder, sinus congestion, pulmonary embolism, interstitial lung disease

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, constipation, vomiting, gastrointestinal haemorrhage, abdominal distention.
	Frequency not known- reported post marketing experience	Constipation, nausea, vomiting, gastrointestinal haemorrhage, abdominal distention, diarrhoea, dysphasia, dry mouth, duodenal ulcer, gastrointestinal disorder, peptic ulcer, rectal polyp
Hepato-biliary disorders	Frequency not known- reported post marketing experience	Hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Frequent	Erythema, alopecia, dry skin, hyperhidrosis, rash, urticaria, abnormal hair growth, hair disorder, night sweats, hypotrichosis, pigmentation disorder, cold sweats, hirsutism
	Frequency not known- reported post marketing experience	Alteration in skin sensation, chills, rash Alopecia, ecchymosis, dry skin, photosensitivity reaction, urticaria, dermatitis, hair growth abnormal, pruritus,

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
		pigmentation disorder, skin legion
Musculoskeletal and connective tissue disorders	Frequent	Bone pain, myalgia, bone swelling
	Frequency not known - reported post marketing experience	Myalgia, bone swelling, arthropathy arthralgia, ankylosing spondylitis, tenosynovitis
Renal and urinary disorders	Frequent	Haematuria
	Frequency not known - reported post marketing experience	Urinary incontinence, pollakiuria, micturition urgency, haematuria, bladder spasm, urinary tract disorder, urinary tract obstruction
Reproductive system and breast disorders	Frequent	Gynaecomastia, breast tenderness, erectile dysfunction, testicular pain, breast enlargement, breast pain, prostate pain, penile swelling, penis disorders, testis atrophy, penile blister

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
	Frequency not known- reported post marketing experience	Gynaecomastia, breast tenderness, testicular atrophy, breast pain, testicular disorder, penile swelling, penis disorder, prostatic pain
General disorders and administration site conditions	Frequent	Mucosal dryness, Pain, oedema, asthenia, fatigue, pyrexia
	Frequency not known- reported post marketing experience	Pain, oedema, asthenia, pyrexia, injection site reaction, injection site inflammation, injection site pain, injection site induration, injection site abscess sterile, injection site haematoma, chills, nodules, thirst, inflammation, pelvic fibrosis
Investigations	Frequent	PSA increased, bone density decreased, diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis, haematocrit decreased, haemoglobin decreased,

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
		blood urea increased, blood creatinine increased
	Less frequent	increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time, increased weight.
	Frequency not known- reported post marketing experience	Increased blood urea, increased blood uric acid, increased blood creatinine, increased blood calcium, abnormal electrocardiogram, ECG signs of myocardial ischaemia, decreased platelet count, abnormal liver function test, decreased blood potassium, increased white blood cell count, decreased white blood cell count, prolonged prothrombin time (increased INR), prolonged activated partial thromboplastin time, cardiac murmur, increased low density lipoprotein, increased blood

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
		triglycerides, increased blood bilirubin
Injury, poisoning and procedural complications	Frequency not known- reported post marketing experience	Spinal fracture

c. **Description of selected 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. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the non-treated control group. 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 gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of 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.
See section 4.4 and 4.5 for precautions regarding laboratory tests and pre-existing conditions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

It is expected that the symptoms of overdosage of **GENPROLEX** will be in line with the reported adverse effects (see section 4.8).
Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Gonadotropin releasing hormone analogues, ATC code: L02AE02

A 21.10 – Trophic hormones

Mechanism of action

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural

hormone.

Leuprolide acetate, a GnRH agonist, acts as an inhibitor of gonadotropin secretion. Animal studies indicate that following an initial stimulation, continuous administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect was reversible upon discontinuation of drug therapy.

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 levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and oestrone and oestradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate or pre-pubertal levels. In pre-menopausal females, oestrogens are reduced to post-menopausal levels. These decreases occur within a month after initiating of treatment at recommended doses.

5.2. Pharmacokinetic properties

Absorption

Leuprolide acetate is not active when given orally.

Bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of approximately three hours.

Distribution

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

Biotransformation

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7,6 L/h, with a terminal elimination half-life of approximately three hours based on a two compartment model.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in five prostate cancer patients reached maximum concentration two to six hours after dosing and were approximately 6 % of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20 % of mean leuprolide concentrations.

Elimination

Following administration of leuprolide acetate for depot suspension, 3,75 mg to three patients, less than 5 % of the dose was recovered as parent and M-I metabolite in the urine over 27 days.

Special Populations

Renal impairment

The pharmacokinetics of the drug in renally impaired patients has not been determined.

Hepatic impairment

The pharmacokinetics of the drug in hepatically impaired patients has not been determined.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

GENPROLEX injection contains the following inactive ingredients:

Sodium chloride, benzyl alcohol, glacial acetic acid, sodium hydroxide, water for injection.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

GENPROLEX is supplied in a multi-use glass vial Tubular Type-I, 6R clear BB vial with 20 mm neck, stoppered with 20 mm grey bromobutyl rubber stopper and sealed with aluminium seal having sky blue colour PP disc. The Vial is packed in pre-printed carton with package leaflet.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

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8. REGISTRATION NUMBER

54/21.10/0089

9. DATE OF FIRST AUTHORISATION

24 October 2023

10. DATE OF REVISION OF TEXT

N/A