PROFESSIONAL INFORMATION FOR PRINOLID 7,5

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRINOLID 7,5 7,5 mg Lyophilised microspheres for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRINOLID 7,5: Each vial contains 7,5 mg leuprolide acetate.

When reconstituted with the sterile solvent, the suspension contains 7,5 mg/mL leuprolide acetate.

Excipient(s) with known effect:

Contains sugar (mannitol): 13,20 mg per vial lyophilised powder.

Contains sugar (mannitol): 75,0 mg per vial sterile solvent.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for injection and solvent for reconstitution.

Powder

White powder without discoloration or superficial foreign particles.

Solvent

Limpid, colourless liquid, without suspended particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRINOLID 7,5 is indicated for the palliative treatment of advanced prostate cancer.

4.2 Posology and method of administration

Posology

The recommended dose is 1 injection (7,5 mg) every month.

Special populations

Paediatric population

No data are available.

Method of administration

PRINOLID 7,5 is administered subcutaneously and provide continuous release of leuprolide acetate over a one-, three, four- or six-month treatment period. The injection delivers the dose of leuprolide acetate as lyophilised microspheres.

General

The injection sites should be varied periodically.

For information on instructions for preparation or reconstitution see section 6.6

4.3 Contraindications

- Hypersensitivity to leuprolide acetate or similar nonapeptides or to any of the excipients listed in section 6.1 or to synthetic gonadotrophin releasing hormone (Gn-RH) or Gn-RH derivatives.
- PRINOLID 7,5 is contraindicated in women and in paediatric patients, and was not studies in women or children (see section 4.6).

- In patients who previously underwent orchiectomy (as with other GnRH agonists, PRINOLID 7,5 does not result in further decrease of serum testosterone in case of surgical castration).
- As sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastases (see also section 4.4).

4.4 Special warnings and precautions for use

Correct reconstitution

Lack of clinical efficacy may occur due to incorrect reconstitution of the product. See section 6.6 for the instructions for preparation and administration of the product and for evaluation of testosterone levels in
cases of suspected or known handling errors.

Androgen deprivation therapy may prolong the QT interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicines that might prolong the QT interval (see section 4.5) medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating PRINOLID 7,5.

Cardiovascular diseases

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 GnRH agonists should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Transient testosterone flare

Leuprolide acetate causes a transient increase in serum concentrations of testosterone, dihydrotestosterone and acid phosphatase during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, haematuria, or ureteral or bladder outlet obstruction (see section 4.8). These symptoms usually subside on continuation of therapy.

Additional administration of an appropriate antiandrogen should be considered beginning 3 days prior to leuprolide therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone.

Following surgical castration, PRINOLID 7,5 does not lead to a further decrease in serum testosterone levels in male patients.

Bone density

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with GnRH agonists (see section 4.8).

Antiandrogen therapy significantly increases the risk for fractures owing to osteoporosis. Only limited data is available on this issue. Fractures owing to osteoporosis were observed in 5 % of patients following 22 months of pharmacological androgen deprivation therapy and in 4 % of patients following 5 to 10 years of treatment. The risk for fractures owing to osteoporosis is generally higher than the risk for pathological fractures.

Apart from long lasting testosterone deficiency, increased age, smoking and consumption of alcoholic beverages, obesity and insufficient exercise may have an influence on the development of osteoporosis.

Pituitary apoplexy

During post-marketing surveillance, cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of GnRH-agonists, with a majority occurring within 2 weeks of the first dose, and some within

the first hour. In these cases, pituitary apoplexy was presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention is required.

Hyperglycaemia and diabetes

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.

Convulsions

Post marketing reports of convulsions have been observed in patients on leuprolide acetate therapy with or without a history of predisposing factors. Convulsions are to be managed according to the current clinical practice.

Other events

Cases of ureteral obstruction and spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with GnRH agonists. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Patients with vertebral and/or brain metastases as well as patients with urinary tract obstruction should be closely monitored during the first few weeks of therapy.

4.5 Interactions with other medicines and other forms of interaction

No pharmacokinetic interaction studies have been performed with PRINOLID 7,5.

There have been no reports of any interactions of leuprolide acetate with other medicines.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of PRINOLID 7,5 with medicines known to prolong the QT interval or medicines able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Medicine/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.

4.6 Fertility, pregnancy and lactation

Leuprolide can cause foetal harm when administered to pregnant women. Major foetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There were increased foetal mortality and decreased foetal weights in rats and rabbits. The effects on foetal mortality are expected consequences of the alterations in hormonal levels brought about by this medicine. The possibility exists that spontaneous abortion may occur.

4.7 Effects on ability to drive and use machines

No studies on the effects of PRINOLID 7,5 on the ability to drive and use machines have been performed. The ability to drive and operate machines may be impaired due to fatigue, dizziness and visual disturbances being possible side effects of treatment or resulting from the underlying disease.
It is not always possible to predict to what extent PRINOLID 7,5 may interfere with the daily activities of a patient.
Patients should ensure that they do not engage in the above activities until they are aware of the measure to which PRINOLID 7,5 affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions seen with leuprolide acetate are mainly subject to the specific pharmacological action of leuprolide acetate, namely increases and decreases in certain hormone levels.

PRINOLID 7,5 may cause a transient increase in serum testosterone during the first, one to two weeks of treatment. Potential exacerbation of signs and symptoms may therefore be of concern, during the first few weeks of treatment, in patients with vertebral metastases and/or urinary obstruction or haematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms (see section 4.4).

The most commonly reported adverse reactions are hot flashes, nausea, malaise and fatigue and transient local irritation at the site of injection. Mild or moderate hot flashes occur in approximately 58 % of patients.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequent	Nasopharyngitis.
	Less frequent	Urinary tract infection, local skin infection.
Blood and lymphatic system disorders	Frequent	Haematology changes, anaemia.
	Frequency not known	Thrombocytopenia, leucopenia

Immune system disorders	Frequency not known	Anaphylactic/anaphylactoid reactions
Metabolism and nutrition disorders	Less frequent	Aggravated diabetes mellitus.
Psychiatric disorders	Less frequent	Abnormal dreams, depression, decreased libido
	Frequency not known	Amnesia
Nervous system disorders	Less frequent	Dizziness, headache, hypoaesthesia, insomnia, taste disturbance, smell disturbance, vertigo, abnormal involuntary movements.
	Frequency not known	Convulsions, infarction of pre-existing pituitary apoplexy
Eye disorders	Frequency not known	Visual disturbances
Cardiac disorders	Frequency not known	QT prolongation (see sections 4.4 and 4.5), palpitations
Vascular disorders	Frequent	Hot flushes.
	Less frequent	Hypertension, hypotension, syncope, collapse.
	Frequency not known	Peripheral oedema
Respiratory, thoracic and	Less frequent	Rhinorrhoea, dyspnoea
	Frequency not known	Interstitial lung disease, pulmonary embolism

mediastinal disorders		
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, gastroenteritis/colitis, constipation, dry mouth, dyspepsia, vomiting.
	Less frequent	Flatulence, eructation.
Skin and subcutaneous tissue disorders	Frequent	Ecchymoses, erythema, pruritus, night sweats.
	Less frequent	Clamminess, increased sweating, alopecia, skin eruption.
	Frequency not known	Alteration in skin sensation, chills, rash
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, limb pain, myalgia, rigors, weakness.
	Less frequent	Back pain, muscle cramps.
	Frequency not known	Muscular atrophy
Renal and urinary disorders	Frequent	Urinary infrequency, difficulty in micturition, dysuria, nocturia, oliguria.
	Less frequent	Bladder spasm, haematuria, aggravated urinary frequency, urinary retention.

Reproductive system and breast disorders	Frequent	Breast tenderness, testicular atrophy, testicular pain
	Less frequent	infertility, breast hypertrophy, erectile dysfunction, reduced penis size.
		Breast pain, gynaecomastia, impotence, testicular disorder.
General disorders and administration site conditions	Frequent	Fatigue, injection site burning, injection site paraesthesia, malaise, injection site pain, injection site bruising, injection site stinging.
	Less frequent	Injection site pruritus, injection site induration, lethargy, pain, pyrexia, injection site ulceration and necrosis.
Investigations	Frequent	Increased blood creatinine phosphokinase, prolonged coagulation time.
	Less frequent	increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time, increased weight.

c. Description of selected adverse reactions

Convulsions have been reported after GnRH agonist analogue administration (see section 4.4).

Local adverse events reported after injection of leuprolide 7,5 mg are similar to the local adverse events associated with similar subcutaneously injected products. Generally, these localised adverse events following subcutaneous injection are mild and described as being of brief duration.

Anaphylactic/anaphylactoid reactions have been reported rarely after GnRH agonist analogue administration.

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 a GnRH analogue. It can be anticipated that long periods of treatment with leuprolide may show increasing signs of osteoporosis. Regarding the increased risk for fractures owing to osteoporosis (see section 4.4).

Exacerbation of signs and symptoms of the disease

Treatment with leuprolide acetate can cause exacerbations of signs and symptoms of the disease during the first few weeks. If conditions such as vertebral metastases and/or urinary obstruction or haematuria are aggravated, neurological problems such as weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms may occur.

d. Paediatric population

No information.

e. Other special population(s)

No information.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There are no reports of abuse or overdose having occurred in clinical practice with leuprolide acetate, but in the event that excessive exposure becomes a reality, observation and symptomatic supportive treatment are recommended.
In clinical trials using daily subcutaneous injections of leuprolide acetate in patients with prostate cancer, doses as high as 20 mg / day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.10 – Tropic hormones

ATC code: L02AE 02

Leuprolide acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH).

Mechanism of action

Leuprolide acetate, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis in males. This effect is reversible upon discontinuation of medicinal product therapy. However, the agonist possesses greater potency than the natural hormone and the time to recovery of testosterone levels may vary between patients.

Administration of leuprolide acetate results in an initial increase in circulating levels of luteinising hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids, testosterone and dihydrotestosterone in males. Continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL). These decreases occur within three to five weeks after initiation of treatment. Mean testosterone levels at six months are 6,1 (± 0,4) ng/dL, comparable to levels following bilateral orchiectomy. In the vast majority of patients, the testosterone levels seen were below 20 ng/dL although the full benefit of these low levels has not yet been established. PSA levels decreased by 94% over six months.

Long-term studies have shown that continuation of therapy maintains testosterone below the castrate level for up to seven
years, and presumably indefinitely.

5.2 Pharmacokinetic properties

Absorption

In patients with advanced carcinoma of the prostate, mean serum leuprolide concentrations following the initial injection rise to 25,3 ng/mL at 4-8 hr (C_{max}) after injection. After the initial increase following each injection (the plateau phase from 2-28 days after each dose), serum concentrations remain relatively constant (0,28 – 1,67 ng/mL). There is no evidence of accumulation during repeated dosing.

Distribution

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

Elimination

In healthy male volunteers, a 1 mg bolus of leuprolide acetate administered intravenously revealed that the mean systemic clearance was 8,34 l/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

No excretion studies have been conducted with PRINOLID 7,5.

No medicine metabolism study was conducted with PRINOLID 7,5.

5.3 Preclinical safety data

Preclinical studies with leuprolide acetate, revealed in both sexes effects on the reproductive system, which were expected from the known pharmacological properties. These effects were shown to be reversible after discontinuation of the treatment and an appropriate period of regeneration. Leuprolide acetate did not show teratogenicity. Embryotoxicity/lethality was observed in rabbits, in line with the pharmacological effects of leuprolide acetate on the reproductive system.

Carcinogenicity studies were performed in rats and mice over twenty-four months. In rats, a dose-related increase in pituitary apoplexy was observed after subcutaneous administration at doses of 0,6 to 4 mg/kg/day.

No such effect was observed in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilised powder

Gelatin

Mannitol

Polylactic acid (PLA)

Solvent

Carmellose sodium 30 cps

Mannitol

Polysorbate 80

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder

36 months.

Store at or below 30 °C and protect from light.

Solvent

36 months.

Store at or below 30 °C.

6.4 Special precautions for storage

Reconstituted suspension: Since PRINOLID 7,5 microspheres and its solvent contains no preservative, the reconstituted suspension should be used immediately after preparation and any unused portion should be discarded.

6.5 Nature and contents of container

Powder

Single dose administration kit containing one 6 mL clear type I glass vial, with a 20 mm dark grey rubber stopper and aluminium crimp cap with blue plastic flip cap; 1 solvent ampoule; 1 disposable syringe and two 22 G 1½ needles.

Solvent

3 mL colourless glass ampoule type I with a nominal volume of 2 mL, with a breakage ring and specified dimensions, is used.

6.6 Special precautions for disposal

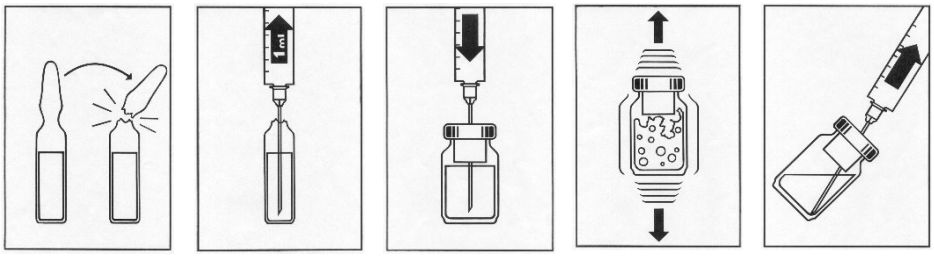
Discard the needle in an appropriate manner (i.e. medical sharps waste bin).

Preparation of administration

The vial of PRINOLID 7,5 should be reconstituted immediately prior to administration in accordance with the following directions:

1. Verify that all the content of the ampoule is in its body. Press to open the ampoule's neck. (A)
2. Using the provided syringe with needle, extract 2 mL of the solvent using aseptic technique. (B)
   Discard the rest of the liquid.
3. Remove the cover of the vial and inject the solvent in the vial. (C)
4. Shake the vial thoroughly to disperse particles and to obtain a uniform milky suspension. (D)
5. Extract all the contents of the vial by slightly inclining it and putting the needle's bevel in the bottom. Do not invert the vial. (E).
6. Disinfect the skin in the place where the injection will be applied and inject the content of the syringe using the second needle provided with the kit.

No other fluid should be used for reconstitution of PRINOLID 7,5.



A B C D E

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane

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2144

8. REGISTRATION NUMBER(S)

55/21.10/0734

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT