PROFESSIONAL INFORMATION FOR PRINOLID 11,25

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRINOLID 11,25 11,25 mg Lyophilised microspheres for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRINOLID 11,25: Each vial contains 11,25 mg leuprolide acetate.

When reconstituted with the sterile solvent, the suspension contains 11,25 mg/mL leuprolide acetate.

Excipient(s) with known effect:

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

Contains sugar (mannitol): 100 mg per vial sterile solvent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized 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

Prostate Cancer

PRINOLID 11,25 is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration is either not indicated or unacceptable to the patient.

Endometriosis

PRINOLID 11,25 is indicated in the treatment of endometriosis for a period of six months. It can be used as sole therapy or as an adjunct to surgery.

Uterine Fibroids

PRINOLID 11,25 is also indicated in the treatment of leiomyoma uteri (uterine fibroids) for a period up to six months. Therapy may be preoperative prior to myomectomy or hysterectomy, or it may provide symptomatic relief for the perimenopausal woman who does not desire surgery.

Breast Cancer

PRINOLID 11,25 is indicated as adjuvant therapy to surgery in breast carcinomas.

4.2 Posology and method of administration

PRINOLID 11,25 must be administered under the supervision of a medical practitioner.

Posology

Prostate cancer

The recommended dose of PRINOLID 11,25 in the palliative treatment of advanced prostatic carcinoma is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

Endometriosis/Uterine fibroids

The recommended dose of PRINOLID 11,25 in the treatment of endometriosis and uterine fibroids is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

Breast Cancer

The recommended dose of PRINOLID 11,25 as adjuvant therapy to surgery in breast carcinoma is 11,25 mg administered as a single subcutaneous or intramuscular injection every 3 months.

Special populations

Paediatric population

No data are available.

Method of administration

For subcutaneous or intramuscular use.

General

The reconstituted suspension should be used immediately after preparation and any unused reconstituted suspension should be discarded, as the product has not been shown to be stable for 24 hours after reconstitution (see section 6.4).

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 of PRINOLID 11,25 listed in section 6.1 or to synthetic gonadotrophin releasing hormone (Gn-RH) or Gn-RH derivatives.

Woman:

- PRINOLID 11,25 is contra-indicated in women who are, or may become pregnant while receiving the medicine (see section 4.6).
- PRINOLID 11,25 should not be administered to women who are breastfeeding (see section 4.6).
- PRINOLID 11,25 should not be administered to patients with undiagnosed vaginal bleeding.
- In the pre- and perimenopausal breast cancer setting:
- Initiation of aromatase inhibitor treatment before adequate ovarian suppression with leuprolide has been achieved (see section 4.4).
- Isolated cases of anaphylaxis have been reported with the monthly depot formulation (PRINOLID 11,25) of leuprolide acetate.

4.4 Special warnings and precautions for use

Development or aggravation of diabetes may occur, therefore diabetic patients may require more frequent monitoring of blood glucose during treatment with PRINOLID 11,25.

Epidemiological data have shown that during androgen deprivation therapy changes in the metabolic condition (reduction in glucose tolerance or aggravation of pre-existing diabetes) as well as an increased cardiovascular disease risk may occur. However, data did not confirm the link between treatment with Gonadotropin-releasing hormone (GnRH) analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be monitored.

Hepatic dysfunction and jaundice with elevated liver enzyme have been reported. Therefore, close observation should be made and appropriate measures taken if necessary.

Spinal fracture, paralysis and hypotension have been reported.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as leuprolide. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Convulsions

Post-marketing reports of seizures have been observed in patients treated with leuprolide acetate and these events have been reported in adults, and in those with or without a history of epilepsy, seizure disorders or risk disorders for seizures, cerebrovascular disorders, central nervous system anomalies or tumours and in patients on concomitant medicines that have been associated with convulsions such as bupropion and Selective Serotonin Reuptake Inhibitors (SSRIs).

Men

In the initial stages of therapy, a transient rise in levels of testosterone, dihydrotestosterone and acid phosphatase may occur. In some cases, this may be associated with a “flare” or exacerbation of the tumour growth resulting in temporary deterioration of the patient's condition. These symptoms usually subside on continuation of therapy. “Flare” may manifest itself as systemic or neurological symptoms in some cases.
In order to reduce the risk of “flare”, an anti-androgen may be administered beginning 3 days prior to leuprolide acetate 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.

In the event of an abscess occurring at the injection site, testosterone level should be monitored as there may be inadequate absorption of leuprolide from the depot formulation.
Patients at risk of ureteric obstruction or spinal cord compression (metastatic vertebral lesions) should be considered carefully and closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens. Should urological/neurological complications occur, these should be treated by appropriate specific measures.
Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss which, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture.
If an anti-androgen is used over a prolonged period, due attention should be paid to the contra-indications and precautions associated with its extended use.
Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long term clinical studies with leuprolide acetate.
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 (such as class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antidysrhythmic medications)) medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating PRINOLID 11,25 (see section 4.5).
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 GnRH agonists, and manage with current practice for treatment of hyperglycaemia or diabetes.

Women

Endometriosis/Uterine Fibroids

During the early phase of endometriosis therapy, sex steroids temporarily rise above baseline because of the physiological effect of the medicine. Therefore, a worsening of clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

When receiving GnRH analogues for the treatment of endometriosis, the addition of HRT (an estrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms.

The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. The extent of bone demineralisation due to hypo-estrogenaemia is proportional to time and, consequently, is the adverse event responsible for limiting the duration of therapy to 6 months. The generally accepted level of bone loss with LHRH analogues such as PRINOLID 11,25 is 5%. In clinical studies with PRINOLID 11,25 the levels varied between 2,3 % and 15,7 % depending on the method of measurement. During one six-month treatment period, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of medicine that can reduce bone mass such as anticonvulsants or corticosteroids, PRINOLID 11,25 therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with PRINOLID 11,25 is instituted.

In women with submucous fibroids there have been reports of severe bleeding following administration of PRINOLID 11,25 as a consequence of the acute degeneration of the fibroids. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required.

PRINOLID 11,25 may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures. Reports of heavy vaginal bleeding requiring medical or surgical intervention with continued therapy have been reported in the treatment of submucous leiomyoma uteri.

PRINOLID 11,25 is not a contraceptive. If contraception is required, a non-hormonal method of contraception should be used.

Breast cancer

Advanced and early breast cancer

In order to ensure adequate ovarian suppression in pre- and perimenopausal women, treatment with PRINOLID 11,25 should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor, and 3 monthly leuprolide injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment. Women who are premenopausal at breast cancer diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued estrogen production from the ovaries. Irrespective of menstrual status, premenopausal status should be confirmed following chemotherapy and before commencement of PRINOLID 11,25, by blood concentrations of estradiol and FSH within the reference ranges for premenopausal women, in order to avoid unnecessary treatment with PRINOLID 11,25 in the event of a chemotherapy-induced menopause.

Following commencement of PRINOLID 11,25, it is important to confirm adequate ovarian suppression (gonadotrophin analogue- induced menopause) by serial assessment of circulating FSH, and estradiol if this subset of women is to be considered for therapy with an aromatase inhibitor, in accordance with current clinical practice recommendations. Accordingly, ovarian suppression should be confirmed by low blood concentrations of FSH and estradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during combination therapy with PRINOLID 11,25 and an aromatase inhibitor. This is to avoid aromatase inhibitor-induced rebound increase in circulating estrogen, with consequential implications for the breast cancer. Of note, circulating FSH levels are lowered in response to gonadotrophin analogue-induced ovarian

suppression (induced menopause), unlike in a natural menopause where FSH levels are elevated.

Patients who have discontinued PRINOLID 11,25 treatment should also discontinue aromatase inhibitors within 3 months of the last PRINOLID 11,25 administration.

Particular attention should also be paid to the prescribing information of co-administered medicines, such as aromatase inhibitors, tamoxifen, CDK4/6 inhibitors, for relevant safety information when administered in combination with leuprolide.

Bone mineral density should be assessed before starting treatment with PRINOLID 11,25, particularly in women who have additional risk factors for osteoporosis. These patients should be closely monitored and treatment for, or prophylaxis of, osteoporosis should be initiated when appropriate.

The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when a GnRH agonist is used in combination with either an aromatase inhibitor or tamoxifen is approximately 89 % with the aromatase inhibitor and approximately 76 % with tamoxifen.

Hypertension has been reported as a targeted adverse event at a very common frequency with GnRH agonist in combination with either exemestane or tamoxifen.

Premenopausal women with breast cancer receiving GnRH agonist in combination with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as targeted adverse events at a common frequency with a GnRH agonist in combination with either exemestane or tamoxifen.

Premenopausal women with breast cancer receiving a GnRH agonist in combination with either exemestane or tamoxifen should have regular monitoring of risk factors for diabetes with blood glucose monitoring on a regular basis and appropriate anti-diabetic treatment initiated, if appropriate, according to national guidelines.

Depression has been reported to occur in approximately 50 % of patients treated with a GnRH agonist in combination with either tamoxifen or exemestane, but less than 5 % of patients had severe depression (grade 3-4). Patients should be informed accordingly and

treated as appropriate if symptoms occur. Patients with known depression or depression history should be carefully monitored during therapy.
Treatment of premenopausal women with endocrine responsive early stage breast cancer with leuprolide in combination with tamoxifen or an aromatase inhibitor should follow a careful individual appraisal of the risks and benefits.

Changes in Laboratory Values During Treatment

Liver Enzymes

Three percent of uterine fibroid patients treated with PRINOLID 11,25, manifested post-treatment transaminase values that were at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

Lipids

Triglycerides were increased above the upper limit of normal in 32 % of the endometriosis patients who received PRINOLID 11,25. Of those endometriosis and uterine fibroid patients whose pre-treatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in endometriosis patients and +11 mg/dL to +29 mg/dL in uterine fibroid patients. In the endometriosis treated patients, increases from the pre-treatment values were statistically significant ($p<0,03$).

Impairment of fertility

Studies in adults with leuprolide acetate and similar analogues have shown full reversibility of fertility suppression when the medicine is discontinued after continuous administration for periods of up to 24 weeks.

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been performed.

Medicine interactions

Pharmacokinetic-based interaction studies have not been conducted with PRINOLID 11,25. However, due to leuprolide acetate being a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes, and due to this compound being only 46 % bound to plasma proteins, medicine interactions are not expected to occur.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of PRINOLID 11,25 with medicines known to prolong the QT interval or medicines that is able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Laboratory tests

Response to PRINOLID 11,25 used in the palliative treatment of advanced prostatic cancer, should be monitored by measuring serum levels of testosterone and acid phosphatase. 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. Castrate levels were reached within two to four weeks and once achieved was maintained for as long as the patients received their injections.

Medicine/Laboratory Test Interactions

Administration of leuprolide acetate in women resulted in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after PRINOLID 11,25 treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of PRINOLID 11,25 may be misleading.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When used 3-monthly at the recommended dose, PRINOLID 11,25 usually inhibits ovulation and stops menstruation.

Contraception is not ensured by taking PRINOLID 11,25, therefore patients should use non-hormonal methods of contraception during treatment.

Patients should be advised that if they miss successive doses of PRINOLID 11,25, breakthrough bleeding or ovulation may occur with the potential for conception. Patients should be advised to see their medical practitioner if they believe they may be pregnant. If a patient becomes pregnant during treatment, the medicine must be discontinued. The patient must be apprised of this evidence and the potential for an unknown risk to the foetus.

Pregnancy

PRINOLID 11,25 is contraindicated during pregnancy (see section 4.3)

The safe use of PRINOLID 11,25 in pregnancy has not been established clinically.

Studies in animals have shown reproductive toxicity (see section 5.3). Before starting treatment with PRINOLID 11,25, pregnancy must be excluded. There have been reports of foetal malformation when PRINOLID 11,25 has been given during pregnancy.

Breastfeeding

It is not known whether PRINOLID 11,25 is excreted in human milk. Therefore, PRINOLID 11,25 should not be used in women who are breastfeeding.

4.7 Effects on ability to drive and use machines

PRINOLID 11,25 can influence the ability to drive and use machines due to visual disturbances and dizziness.

It is not always possible to predict to what extent PRINOLID 11,25 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 11,25 affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions seen with PRINOLID 11,25 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

Men

In cases where a "tumour flare" occurs after PRINOLID 11,25 therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction, weakness of the lower extremities and paraesthesia.

These symptoms subside on continuation of therapy.

Women

Those adverse events occurring most frequently with PRINOLID 11,25 are associated with hypo-estrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe), and vaginal dryness.

Estrogen levels return to normal after treatment is discontinued.

The induced hypo-estrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible (see section 4.4).

Vaginal haemorrhage may occur during therapy due to acute degeneration of submucous fibroids (see section 4.4).

b. Tabulated summary of adverse reactions

Men

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	Prostate tumor flare, aggravation of prostate cancer
Blood and lymphatic system disorders	Frequency not known	Anaemia (reported in medicines of this class), thrombocytopaenia,leucopoenia.
Immune system disorders	Frequency not known	Hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions).
Metabolism and nutrition disorders	Frequent	Decreased appetite, weight fluctuation.
	Frequency not known	Lipids abnormal, glucose tolerance abnormal.
Psychiatric disorders	Frequent	Insomnia, depression (see section 4.4), mood changes (long-term use)**
	Less frequent	Mood changes (short-term use)**

Nervous system disorders	Frequent	Headache (occasionally severe).
	Less frequent	Dizziness, paraesthesia, pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma.
	Frequency not known	Paralysis (see section 4.4), seizure
Eye disorders	Frequency not known	Visual impairment.
Cardiac disorders	Frequency not known	Palpitations, electrocardiogram QT prolonged (see sections 4.4 and 4.5).
Vascular disorders	Frequent	Hot flush, vasodilation.
	Frequency not known	Pulmonary embolism, hypertension, hypotension (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Frequency not known	Interstitial lung disease
Gastrointestinal disorders	Frequent	Nausea.
	Less frequent	Diarrhoea, vomiting.
Hepatobiliary disorders	Frequent	Hepatic function abnormal, liver function test abnormal (usually transient).
	Frequency not known	Jaundice.

Skin and subcutaneous tissue disorders	Frequent	Dry skin, hyperhidrosis, rash, urticaria, hair growth abnormal, hair disorder, night sweats, hypotrichosis, pigmentation disorder, cold sweat, hirsutism.
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle weakness, bone pain.
	Less frequent	Myalgia, weakness of lower extremities.
	Frequency not known	Spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists.
Renal and urinary disorders	Frequency not known	Urinary tract obstruction
Reproductive system and breast disorders	Frequent	Breast tenderness, breast pain, erectile dysfunction, gynaecomastia, libido decreased, penile swelling, penis disorder, prostate pain, testicular atrophy, testicular pain.
General disorders and administration site conditions	Frequent	Fatigue, injection site reaction (e.g., induration, erythema, pain, abscesses, swelling, mucosal dryness, nodules, ulcers and necrosis), peripheral oedema.
	Frequency not known	Pyrexia.

**mood changes (long term use: “frequent” and short-term use: “less frequent”)

Women

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Blood and lymphatic system disorders	Frequency not known	Anaemia (reported in medicines of this class), thrombocytopaenia, leucopoenia.
Immune system disorders	Frequency not known	Hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions).
Metabolism and nutrition disorders	Frequent	Weight fluctuation.
	Less frequent	Decreased appetite, lipids abnormal.
	Frequency not known	Glucose tolerance abnormal, which may affect diabetic control.
Psychiatric disorders	Frequent	Insomnia, mood altered depression (see section 4.4), loss or decreased libido, affects lability.
Nervous system disorders	Frequent	Headache (occasionally severe), dizziness, paraesthesia.
	Less frequent	Pituitary haemorrhage has been

		reported following initial administration in patients with pituitary adenoma.
	Frequency not known	Paralysis (see section 4.4), seizure
Eye disorders	Less frequent	Visual impairment.
Cardiac disorders	Less frequent	Palpitations.
Vascular disorders	Frequent	Hot flush.
	Frequency not known	Pulmonary embolism, hypertension, hypotension (see section 4.4), vasodilatation.
Respiratory, thoracic and mediastinal disorders	Frequency not known	Interstitial lung disease
Gastrointestinal disorders	Frequent	Nausea.
	Less frequent	Diarrhoea, vomiting.
Hepatobiliary disorders	Less frequent	Liver function test abnormal (usually transient).
	Frequency not known	Hepatic function abnormal, jaundice.
Skin and subcutaneous tissue disorders	Less frequent	Hair loss, acne, seborrhoea, dry skin, urticaria, skin odour abnormal, hyperhydrosis, hair growth abnormal, hirsutism, hair disorder, eczema, nail disorder, night sweats.

Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle weakness.
	Less frequent	Myalgia.
	Frequency not known	Spinal fracture (see section 4.4), reduction in bone mass which may occur with the use of GnRH agonists.
Reproductive system and breast disorders	Frequent	Breast tenderness, vulvovaginal dryness, dysmenorrhoea, menstrual disorder, breast enlargement, breast engorgement, breast atrophy, genital discharge, vaginal discharge, galactorrhea, breast pain, metrorrhagia, menopausal symptoms, dyspareunia, uterine disorder, vaginitis, menorrhagia.
	Frequency not known	Vaginal haemorrhage.
General disorders and administration site conditions	Frequent	Oedema peripheral, injection site reaction (e.g. injection site induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis, feeling hot, irritability.

	Less frequent	Pyrexia, fatigue.
Investigations	Frequent	Bone density decreased.
Long exposure (6 to 12 months)	Frequent	Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis.

Changes in Bone Density

In controlled studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with leuprolide acetate (as in PRINOLID 11,25). In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3,9 % at six months compared with the pre-treatment value.

For those patients who were tested at six or twelve months after discontinuation of therapy, mean bone density returned to within 2 % of pre-treatment. When leuprolide acetate (as in PRINOLID 11,25) was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2,7 % compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed.

The following tables present adverse reactions from endometriosis, uterine fibroid and breast cancer studies.

Endometriosis

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**

Infections and infestation	Less frequent	Infection, pyelonephritis, furuncle.
Metabolism and nutrition disorders	Frequent	Abnormal weight gain, hypercholesterolaemia, abnormal loss of weight.
	Less frequent	Anorexia, increased appetite.
Psychiatric disorders	Frequent	Depression, affect lability, decreased libido, nervousness, insomnia, anxiety, major depression, confusional state, hostility.
	Less frequent	Personality disorder, delusion, thinking abnormal, euphoric mood, apathy.
Nervous system disorders	Frequent	Headache, dizziness, paraesthesia, migraine, hypertonia.
	Less frequent	Somnolence, amnesia, syncope, ataxia.
Eye disorders	Frequent	Visual impairment, amblyopia.
	Less frequent	Eye disorder, eye pain.
Cardiac disorders	Frequent	Palpitations.
	Less frequent	Tachycardia.
Vascular disorders	Frequent	Vasodilatation.

Respiratory, thoracic and mediastinal disorders	Less frequent	Dysphonia, epistaxis.
Gastrointestinal disorders	Frequent	Nausea, constipation, nausea and vomiting, diarrhoea, dry mouth, abdominal pain
	Less frequent	Abdominal distention, dyspepsia, flatulence, gastritis, gingival bleeding.
Hepatobiliary disorders	Less frequent	Liver tenderness.
Skin and subcutaneous tissue disorders	Frequent	Acne, skin reactions, hirsutism, seborrhoea, alopecia, ecchymosis, rash, dry skin, hyperhidrosis.
	Less frequent	Rash maculo-papular, photosensitivity reaction, hair disorder.
Musculoskeletal and connective tissue disorders	Frequent	Arthropathy, arthralgia, back pain, nuchal rigidity, neck pain.
	Less frequent	Myalgia, arthritis.
Reproductive system and breast disorders	Frequent	Breast atrophy, genital discharge, breast pain, pelvic pain.
	Less frequent	Breast enlargement, breast engorgement, galactorrhoea.

General disorders and administration site conditions	Frequent	Oedema, asthenia, pain, chest pain, oedema peripheral, injection site pain, chills, thirst.
	Less frequent	Face oedema, generalised oedema, injection site reaction, injection site mass, injection site hypersensitivity.

Uterine fibroids

Adverse events reported in uterine fibroids studies

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestation	Less frequent	Rhinitis, vulvovaginal candidiasis, influenza.
Metabolism and nutrition disorders	Frequent	Abnormal weight gain, abnormal loss of weight.
	Less frequent	Increased appetite.
Psychiatric disorders	Frequent	Nervousness, decreased libido, affect lability, insomnia, depression.
	Less frequent	Anxiety.
Nervous system disorders	Frequent	Headache, dizziness, paraesthesia, hypertonia.
	Less frequent	Dysgeusia, migraine.
Eye disorders	Less frequent	Conjunctivitis.

Cardiac disorders	Less frequent	Tachycardia.
Vascular disorders	Frequent	Vasodilatation.
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, flatulence, abdominal pain.
	Less frequent	Constipation, vomiting, nausea and vomiting, dry mouth.
Skin and subcutaneous tissue disorders	Frequent	Rash, dry skin, hyperhidrosis.
	Less frequent	Hirsutism, skin odour abnormal, nail disorder, skin discolouration, dermatitis bullous.
Musculoskeletal and connective tissue disorders	Frequent	Arthropathy, arthralgia, back pain.
	Less frequent	Myalgia.
Reproductive system and breast disorders	Frequent	Vaginitis, breast pain.
	Less frequent	Menstrual disorder, pelvic pain, metrorrhagia, menorrhagia.
General disorders and administration site conditions	Frequent	Pain, oedema peripheral, asthenia, injection site pain, chills.
	Less frequent	Chest pain, oedema, injection site mass, condition aggravated.
Investigations	Frequent	Liver function test abnormal.
	Less frequent	Laboratory test abnormal.

Breast cancer

In a comparative study for leuprolide acetate, pre-menopausal breast cancer patients were treated with leuprolide acetate (as in PRINOLID 11,25) and tamoxifen. The following table summarises the adverse events that were considered at least possibly related to leuprolide acetate (as in PRINOLID 11,25)

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestation	Frequent	Nasopharyngitis.
Nervous system disorders	Frequent	Headache, dizziness.
Gastrointestinal disorders	Frequent	Nausea.
Skin and subcutaneous tissue disorders	Frequent	Dermatitis, hyperhidrosis.
General disorders and administration site conditions	Frequent	Pyrexia, injection site pain, injection induration, feeling hot.

Adverse events reported in breast cancer studies

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestation	Less frequent	Upper respiratory tract infection.
Blood and lymphatic system disorders	Less frequent	Leucopenia.
Metabolism and nutrition	Frequent	Appetite increased, abnormal weight

disorders		gain, abnormal loss of weight, appetite decreased.
	Less frequent	Anorexia.
Psychiatric disorders	Frequent	Depression, insomnia, nervousness, mood swings, sleep disorder.
Nervous system disorders	Frequent	Headache, dizziness, dizziness postural, paraesthesia, somnolence, memory impairment, hypoaesthesia, tremor.
Eye disorders	Frequent	Conjunctivitis.
Ear and labyrinth disorders	Frequent	Deafness, motion sickness, auricular swelling.
Cardiac disorders	Frequent	Palpitations.
Vascular disorders	Frequent	Hot flush.
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis, dyspnoea, sputum increased, cough.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, constipation, abdominal distention, gingivitis, gastritis, abdominal pain (upper/lower), stomatitis, retching.
Hepato-biliary disorders	Frequent	Hepatic function abnormal, hepatic steatosis.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, erythema, alopecia, acne, rash, eczema.

Musculoskeletal and connective tissue disorders	Frequent	Back pain, arthralgia, bone pain, osteoarthritis, neck pain, muscular weakness, musculoskeletal stiffness, muscle twitching.
Renal and urinary disorders	Frequent	Pollyuria.
Reproductive system and breast disorders	Frequent	Vaginal discharge, breast pain, metrorrhagia, menopausal symptoms, vaginitis.
General disorders and administration site conditions	Frequent	Asthenia, injection site pain, injection site induration, general physical health deterioration, feeling hot, chest pain, oedema, oedema peripheral, fatigue, pyrexia, injection site reaction, injection site pruritus, injection site erythema, irritability, malaise.
Investigations	Frequent	Occult blood positive.
	Less frequent	Body temperature increased.

Post-marketing experience

Men – Adverse events reported in prostate cancer studies

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequent	Bronchitis, urinary tract infection.

	Less frequent	Infected cyst, viral infection, candidiasis, sepsis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Pseudolymphoma.
Blood and lymphatic system disorders	Frequent	Anaemia.
	Less frequent	Eosinophilia.
Immune system disorders	Less frequent	Hypersensitivity.
Metabolism and nutrition disorders	Frequent	Anorexia, weight fluctuation.
	Less frequent	Hyperglycaemia, hypoglycaemia, dehydration.
Psychiatric disorders	Frequent	Libido decreased, insomnia, depression.
Nervous system disorders	Frequent	Headache, paraesthesia.
	Less frequent	Dizziness, somnolence, tremor, simple partial seizures.
Cardiac disorders	Less frequent	Angina pectoris, cardiac failure, bradycardia, atrioventricular block.
Vascular disorders	Frequent	Hot flush, lymphoedema, hypertension, thrombophlebitis.
	Less frequent	Aneurysm, circulatory collapse, flushing, haematoma.
Respiratory, thoracic and mediastinal	Frequent	Dyspnoea, asthma.
	Less frequent	Cough, chronic obstructive pulmonary disease.

disorders		
Gastrointestinal disorders	Frequent	Constipation, nausea.
	Less frequent	Gastritis.
Hepatobiliary disorders	Less frequent	Hepatitis cholestatic, hepatocellular injury
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, pruritus.
	Less frequent	Alopecia, rash, dry skin.
Musculoskeletal and connective tissue disorders	Frequent	Bone pain, arthralgia, back pain, pain in extremity, muscular weakness.
	Less frequent	Myalgia, muscle spasm.
Renal and urinary disorders	Frequent	Nocturia, dysuria, haematuria.
	Less frequent	Urinary incontinence, pollakiuria, urinary retention, micturition disorder.
Reproductive system and breast disorders	Frequent	Erectile dysfunction, testicular disorder, gynaecomastia.
General disorders and administration site conditions	Frequent	Fatigue, injection site reaction, pain, oedema peripheral, asthenia, injection site mass, injection site pain, influenza like illness, application site oedema.

	Less frequent	Chest pain, gravitational oedema, mucosal dryness, malaise, gait disturbance.
Investigations	Frequent	Prostatic specific antigen increased, blood alkaline phosphatase increased, blood lactic dehydrogenase increased, alanine aminotransferase increased/ALT, aspartate aminotransferase increased/AST, gamma-glutamyltransferase increased, electrocardiogramabnormal.
	Less frequent	Red blood cell sedimentation rate increased, blood testosterone increased.
Injury, poisoning and procedural complications	Less frequent	Fracture, head injury, fall, device occlusion.
Surgical and medical procedures	Less frequent	Tumour excision, transurethral bladder resection, lithotripsy.

Men – Adverse events seen in post-marketing experience

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequency not known	Infection, urinary tract infection, pharyngitis, pneumonia.
Neoplasms	Frequency not	Skin cancer.

benign, malignant and unspecified (including cysts and polyps)	known	
Blood and lymphatic system disorders	Frequency not known	Anaemia.
Immune system disorders	Frequency not known	Anaphylactic reaction.
Endocrine disorders	Frequency not known	Goiter, pituitary apoplexy.
Metabolism and nutrition disorders	Frequency not known	Diabetes mellitus, increased appetite, hypoglycaemia, dehydration, hyperlipidaemia, hyperphosphatemia, hypoproteinaemia.
Psychiatric disorders	Frequency not known	Mood swings, nervousness, libido increased, insomnia, sleep disorder, depression, anxiety, delusion, suicidal ideation, suicide attempt.
Nervous system disorders	Frequency not known	Dizziness, headache, paraesthesia, lethargy, memory impairment, dysgeusia, hypoaesthesia, syncope, neuropathy peripheral, cerebrovascular accident, loss of consciousness, transient ischemic attack, paralysis, neuromyopathy, convulsion.
Eye disorders	Frequency not known	Vision blurred, eye disorder, visual impairment, amblyopia, dry eye.
Ear and labyrinth disorders	Frequency not known	Tinnitus, hearing impaired.

Cardiac disorders	Frequency not known	Cardiac failure congestive, dysrhythmia, myocardial infarction, angina pectoris, tachycardia, bradycardia, sudden cardiac death.
Vascular disorders	Frequency not known	Lymphoedema, hypertension, phlebitis, thrombosis, hypotension, varicose vein.
Respiratory, thoracic and mediastinal disorders	Frequency not known	Pleural rub, pulmonary fibrosis, epistaxis, dyspnoea, haemoptysis, cough, pleural effusion, lung infiltration, respiratory disorder, sinus congestion, pulmonary embolism, interstitial lung disease.
Gastrointestinal disorders	Frequency not known	Constipation, nausea, vomiting, gastrointestinal haemorrhage, abdominal distention, diarrhoea, dysphagia, dry mouth, duodenal ulcer, gastrointestinal disorder, peptic ulcer, rectal polyp.
Hepatobiliary disorders	Frequency not known	Hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Frequency not known	Alopecia, ecchymosis, rash, dry skin, photosensitivity reaction, urticaria, dermatitis, hair growth abnormal, pruritus, pigmentation disorder, skin lesion.
Musculoskeletal and connective tissue disorders	Frequency not known	Myalgia, bone swelling, arthropathy, arthralgia, ankylosing spondylitis, tenosynovitis.
Renal and urinary disorders	Frequency not known	Urinary incontinence, pollakiuria, micturition urgency, haematuria, bladder spasm, urinary tract disorder, urinary tract obstruction.
Reproductive	Frequency not	Gynaecomastia, breast tenderness, testicular atrophy,

system and breast disorders	known	testicular pain, breast pain, testicular disorder, penile swelling, penis disorder, prostatic pain.
General disorders and administration site conditions	Frequency not known	Pain, oedema, asthenia, pyrexia, injection site reaction, injection site inflammation, injection site pain, injection site induration, injection site abscess sterile, injection site hematoma, chills, nodule, thirst, inflammation, pelvic fibrosis.
Investigations	Frequency not known	Blood urea increased, blood uric acid increased, blood creatinine increased, blood calcium increased, 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 triglycerides, increased blood bilirubin.
Injury, poisoning and procedural complications	Frequency not known	Spinal fracture.

Women – Post marketing surveillance

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequency not known	Infection, urinary tract infection, pharyngitis, pneumonia.

Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency not known	Skin cancer.
Blood and lymphatic system disorders	Frequency not known	Anaemia.
Immune system disorders	Frequency not known	Anaphylactic reaction.
Endocrine disorders	Frequency not known	Goiter, pituitary apoplexy.
Metabolism and nutrition disorders	Frequency not known	Diabetes mellitus, increased appetite, hypoglycaemia, dehydration, hyperlipidaemia, hyperphosphatemia, hypoproteinaemia.
Psychiatric disorders	Frequency not known	Mood swings, nervousness, libido increased, insomnia, sleep disorder, depression, anxiety, delusion, suicidal ideation, suicide attempt.
Nervous system disorders	Frequency not known	Dizziness, headache, paraesthesia, lethargy, memory impairment, dysgeusia, hypoaesthesia, syncope, neuropathy peripheral, cerebrovascular accident, loss of consciousness, transient ischemic attack, paralysis, neuromyopathy, convulsion.
Eye disorders	Frequency not known	Vision blurred, eye disorder, visual impairment, amblyopia, dry eye.

Ear and labyrinth disorders	Frequency not known	Tinnitus, hearing impaired.
Cardiac disorders	Frequency not known	Cardiac failure congestive, dysrhythmia, myocardial infarction, angina pectoris, tachycardia, bradycardia, sudden cardiac death.
Vascular disorders	Frequency not known	Lymphoedema, hypertension, phlebitis, thrombosis, hypotension, varicose vein.
Respiratory, thoracic and mediastinal disorders	Frequency not known	Pleural rub, pulmonary fibrosis, epistaxis, dyspnoea, haemoptysis, cough, pleural effusion, lung infiltration, respiratory disorder, sinus congestion, pulmonary embolism, interstitial lung disease.
Gastrointestinal disorders	Frequency not known	Constipation, nausea, vomiting, gastrointestinal haemorrhage, abdominal distention, diarrhoea, dysphagia, dry mouth, duodenal ulcer, gastrointestinal disorder, peptic ulcer, rectal polyp.
Hepatobiliary disorders	Frequency not known	Hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Frequency not known	Alopecia, ecchymosis, rash, dry skin, photosensitivity reaction, urticaria, dermatitis, hair growth abnormal, pruritus, pigmentation disorder, skin lesion.
Musculoskeletal and connective tissue disorders	Frequency not known	Myalgia, bone swelling, arthropathy, arthralgia, ankylosing spondylitis, tenosynovitis.
Renal and urinary	Frequency not	Urinary incontinence, pollakiuria, micturition

disorders	known	urgency, haematuria, bladder spasm, urinary tract disorder, urinary tract obstruction.
Reproductive system and breast disorders	Frequency not known	Gynaecomastia, breast tenderness, testicular atrophy, testicular pain, breast pain, testicular disorder, penile swelling, penis disorder, prostatic pain.
General disorders and administration site conditions	Frequency not known	Pain, oedema, asthenia, pyrexia, injection site reaction, injection site inflammation, injection site pain, injection site induration, injection site abscess sterile, injection site hematoma, chills, nodule, thirst, inflammation, pelvic fibrosis.
Investigations	Frequency not known	Blood urea increased, blood uric acid increased, blood creatinine increased, blood calcium increased, 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 triglycerides, increased blood bilirubin.
Injury, poisoning and procedural complications	Frequency not known	Spinal fracture.

c. Description of selected adverse reactions

No information.

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

No case of overdose has been reported.

There is no clinical experience with the effects of an acute overdose of PRINOLID 11,25 suspension. In cases of overdosage, the patients should be monitored closely and treatment should be symptomatic and supportive (see sections 4.4 and 4.8).

In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site.

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). The analogue possesses greater potency than the natural hormone.

Mechanism of action

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given on a continuous basis and in therapeutic doses. Animal and human studies indicate that following an initial stimulation chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroideogenesis. This effect is reversible on discontinuation of therapy.

Pharmacodynamic effects

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, and esterone and estradiol in pre-menopausal females).

However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH and sex steroids. In males, testosterone is reduced to castrate or prepubertal levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These hormonal changes occur within a month of initiating medicine therapy at recommended doses.

5.2 Pharmacokinetic properties

Leuprolide acetate is not active when given orally. Bioavailability of this medicine following subcutaneous administration is comparable to that after intramuscular administration.

Absorption

Following a single administration of leuprolide acetate depot suspension (3-month, 11,25 mg), a rapid increase of leuprolide acetate concentration was observed. A mean peak leuprolide plasma concentration of 21,82 (± 11,24) ng/mL was observed three hours after injection. Leuprolide acetate reached plateau levels within 7 to 14 days after injection. At week four, a mean leuprolide plasma concentration of 0,26 (± 0,10) ng/mL was noted. It then declined to a mean leuprolide plasma concentration of 0,17 (± 0,18) ng/mL at 12 weeks. Following a single injection of the three-month formulation of leuprolide acetate depot suspension (11,25 mg) in female subjects, a mean plasma leuprolide concentration of 36,3 ng/mL was observed at four hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean level then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide concentration from 3 to 12 weeks was 0,23 ± 0,09 ng/mL.

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.

Animal studies have shown 14C-labeled leuprolide was metabolised into smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further metabolised.

The major metabolite (M-I) plasma concentrations measured in five prostate cancer patients given leuprolide acetate depot suspension reached a maximum concentration two to six hours after dosing and were approximately 6 % of the peak parent medicine 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

Hepatic and renal impairment

The pharmacokinetics of this product has not been determined in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Animal studies have shown that leuprolide acetate has a high acute safety factor. No major overt toxicological problems have been seen during repeated administration. Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long-term clinical studies. No evidence of mutagenicity or teratogenicity has been shown. Animal reproductive studies showed increased foetal mortality and decreased foetal weights reflecting the pharmacological effects of this LHRH agonist.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilized 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

24 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 11,25 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 aqua green 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).

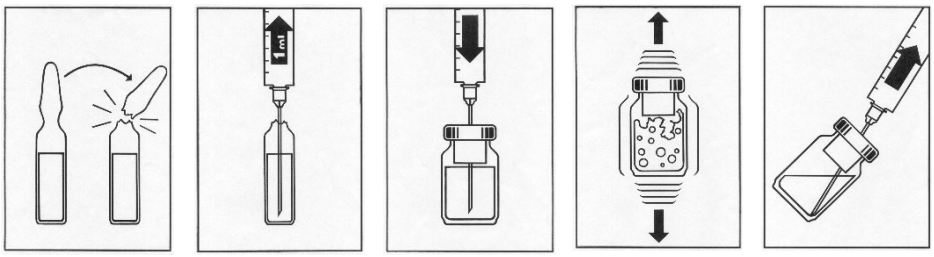
Preparation of administration

The vial of PRINOLID 11,25 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 11,25.



A B C D E

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane

Van Reenens Avenue

Woodmead

2144

8. REGISTRATION NUMBER(S)

55/21.10/0735

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT