PROFESSIONAL INFORMATION FOR PRINOLID 3,75

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRINOLID 3,75 3,75 mg Lyophilised microspheres for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRINOLID 3,75: Each vial contains 3,75 mg leuprolide acetate.

When reconstituted with the sterile solvent, the suspension contains 3,75 mg/ml leuprolide acetate.

Excipient(s) with known effect:

Contains sugar (mannitol): 6,60 mg per vial lyophilised powder.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Powder

White powder without discoloration or superficial foreign particles.

Solvent

Limpid, colourless liquid, without suspended particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

PRINOLID 3,75 is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions, in women of 18 years of age and older, for a period of 6 months.

Prostate Cancer

PRINOLID 3,75 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.

Breast Cancer

PRINOLID 3,75 is indicated as adjuvant therapy to surgery in breast carcinoma.

Central Precocious Puberty

PRINOLID 3,75 is indicated for the treatment of children with central precocious puberty (CPP).

4.2 Posology and method of administration

Posology

EURPRO 3,75 must be administered under the supervision of a medical practitioner.

Endometriosis

The recommended dose of PRINOLID 3,75 in the treatment of endometriosis is 3,75 mg.

Prostate cancer

The recommended dose of PRINOLID 3,75 in the palliative treatment of advanced prostatic carcinoma is 3,75 mg administered subcutaneously once a month.

Breast Cancer

The recommended dose of PRINOLID 3,75 as adjuvant therapy to surgery in breast cancer is 3,75 mg administered 4-weekly as a single subcutaneous or intramuscular injection.

Central Precocious Puberty

The recommended dose of PRINOLID 3,75 for the treatment of children with central precocious puberty must be individualised for each child based on a mg/kg ratio of medicine to body weight. Younger children require higher doses on a mg/kg ratio.

Initial Dose

The recommended starting dose of PRINOLID 3,75 is 0,3 mg/kg for four weeks (minimum 7,5 mg), administered intramuscularly or subcutaneously.

The starting dose will be dictated by the child's weight as follows:

Child's Weight	**Actual Dosage**	**Number of Injections**	**Total Dosage**
≤ 25,0 kg	3,75 mg x 2	1	7,5 mg
25,0 – 37,5 kg	3,75 mg x 3	2	11,25 mg
> 37,5 kg	3,75 mg x 4	2	15,0 mg

Note: When two injections are required to achieve the desired total dosage, they should be administered at the same time.

Maintenance Dose

If total downregulation is not achieved, the dose should be titrated upward in increments of 3,75 mg every four weeks. This dose will be considered the maintenance dose.

The first dose found to result in adequate downregulation can probably be maintained for the

duration of therapy in most children. However, there are insufficient data to guide dosage adjustment as patients move into higher weight categories after beginning therapy at very young ages and low dosages. It is recommended that adequate downregulation be verified in such patients whose weight has increased significantly while on therapy.

The following physiologic effects have been noted with the chronic administration of leuprolide acetate in this patient population:

1. Skeletal Growth: A measurable increase in body length can be noted, since the epiphyseal plates will not close prematurely.
2. Organ Growth: Reproductive organs will return to a prepubertal state.
3. Menses: Menses, if present, will cease.

After one to two months of initiating therapy or changing doses, the child must be monitored with a GnRH stimulation test, determination of sex steroids and Tanner staging to confirm downregulation. Measurements of bone age for advancement should be monitored every 6 to 12 months. The dose should be titrated upward until no progression of the condition is noted either clinically and/or by laboratory parameters.

Discontinuation of PRINOLID 3,75 should be considered before age 11 for females and age 12 for males.

Method of administration

For intramuscular or subcutaneous use.

General

The reconstituted suspension should be used immediately after preparation and any unused portion should be discarded (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 the leuprolide acetate or similar nonapeptides, to any of the excipients of PRINOLID 3,75 listed in section 6.1 or to synthetic gonadotrophin releasing hormone (Gn-RH) or Gn-RH derivatives.
- Children demonstrating hypersensitivity to GnRH, PRINOLID 3,75 or excipients.

Cases of anaphylaxis have been reported with the monthly depot formulation (PRINOLID 3,75) of leuprolide acetate.

Woman:

- PRINOLID 3,75 is contraindicated in women who are, or may become pregnant while receiving the medicine (see section 4.6).
- PRINOLID 3,75 should not be administered to women who are breastfeeding (see section 4.6).
- PRINOLID 3,75 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).

In girls with central precocious puberty:

- PRINOLID 3,75 is contraindicated during pregnancy and lactation.
- PRINOLID 3,75 should not be administered to patients with undiagnosed vaginal bleeding.

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 3,75.

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 both children and 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. Patients may experience a temporary increase in bone pain, which should be managed symptomatically. 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 acetate from the depot formulation.

Cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. Patients at risk of ureteric obstruction or spinal cord compression (those with 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.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases who may develop paraesthesia or paralysis and/or urinary obstruction or haematuria which, if aggravated, may lead to urological problems such as temporary weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms.

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 and Torsade de pointes has been reported. In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicines that might prolong the QT interval, medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating PRINOLID 3,75 (see section 4.5).

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists such as PRINOLID 3,75 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 PRINOLID 3,75 should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists such as LUCRIN DEPOT 3, 75. 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 PRINOLID 3,75, and manage with current practice for treatment of hyperglycaemia or diabetes.

Women

Endometriosis

PRINOLID 3,75 should not be administered to patients with undiagnosed abnormal vaginal bleeding (see section 4.3).

Pregnancy must be excluded before starting with treatment as PRINOLID 3,75 is contraindicated in pregnancy (see section 4.3). When used monthly at the recommended

dose, PRINOLID 3,75 usually inhibits ovulation and stops menstruation. However, taking PRINOLID 3,75 does not ensure contraception. Therefore, patients should use non-hormonal methods of contraception and patients should be advised to see their medical practitioner if they believe they may be pregnant. If a patient becomes pregnant during treatment, PRINOLID 3,75 must be discontinued and the patient must be apprised of the potential risk of the foetus.

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.

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 is 5 %. In clinical studies with leuprolide acetate 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 medicines that can reduce bone mass (such as anticonvulsants or corticosteroids), PRINOLID 3,75 therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with PRINOLID 3,75 is instituted.

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.

Leuprolide acetate may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures.

Breast cancer

Advanced and early breast cancer

In order to ensure adequate ovarian suppression in pre- and peri-menopausal women, treatment with PRINOLID 3,75 should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor, and 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 3,75, by blood concentrations of estradiol and FSH within the reference ranges for premenopausal women, in order to avoid unnecessary treatment with PRINOLID 3,75 in the event of a chemotherapy-induced menopause.

Following commencement of PRINOLID 3,75, 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 3,75 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 3,75 treatment should also discontinue aromatase inhibitors within 1 month of the last PRINOLID 3,75 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 PRINOLID 3,75.

Bone mineral density should be assessed before starting treatment with PRINOLID 3,75, 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 frequently been reported as a targeted adverse event 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.

Precautions

Men:

Patients with urinary obstruction and patients with metastatic vertebral lesions should begin PRINOLID 3,75 therapy under close supervision for the first few weeks of treatment.

Women:

Since menstruation should stop with effective doses of PRINOLID 3,75 the patient should notify her medical practitioner if regular menstruation persists.

In girls with central precocious puberty:

Before starting the therapy, a precise diagnosis of idiopathic and/or neurogenic central precocious puberty is necessary.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with rapidly advancing central precocious puberty.

The therapy is a long-term treatment, adjusted individually. PRINOLID 3,75 should be administered as precisely as possible in regular monthly periods. An exceptional delay of the injection date for a few days (30 ± 2 days) does not influence the results of the therapy.

Response to PRINOLID 3,75 should be monitored one to two months after the start of therapy, with a GnRH stimulation test and sex steroid levels. Measurement of bone age for advancement should be done every 6 to 12 months.

The duration of treatment depends on the clinical parameters at the start of treatment or during the course of treatment (final height prognosis, growth velocity, bone age and/or bone age acceleration) and is decided by the treating paediatrician together with the legal guardian and, if appropriate, the treated child.

It is recommended to use the lowest volumes possible for injections in children in order to decrease the inconvenience which is associated with the intramuscular/subcutaneous

injection.

In the event of a sterile abscess at the injection site (mostly reported after intramuscular injection of higher than the recommended dosage) the absorption of leuprolide acetate from the depot can be decreased. In this case the hormonal parameters (testosterone, estradiol) should be monitored at 2-week intervals and PRINOLID 3,75 should be administered subcutaneously.

The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

The occurrence of vaginal bleeding, spotting and discharge after the first injection may occur as a sign of hormone withdrawal in girls. Vaginal bleeding beyond the first/second month of treatment needs to be investigated.

Bone mineral density (BMD) may decrease during GnRH therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

In girls with bone maturation of older than 12 years and boys with bone maturation of older than 13 years discontinuation of treatment should be considered taking into account the clinical parameters.

Slipped femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

In girls, pregnancy should be excluded before the start of treatment. The occurrence of pregnancy during treatment cannot be generally excluded. In such cases, medical advice should be sought.

Information for parents

Prior to starting therapy with PRINOLID 3,75, the parent(s) or guardian(s) must be made aware of the importance of continuous therapy. Adherence to four-week medicine administration schedules must be complied with if therapy is to be successful. Noncompliance with the treatment regimen or inadequate dosing may result in inadequate control of the pubertal process. The consequences of poor control include the return of pubertal signs such as menses, breast development, and testicular growth. The long-term consequences of inadequate control of gonadal steroid secretion are unknown but may include a further compromise of adult stature.

- During the first two months of therapy, a female may experience menses or spotting. If bleeding continues beyond the second month, notify the medical practitioner.
- Any irritation at the injection site should be reported to the medical practitioner immediately.
- Any unusual signs or symptoms should be reported to the medical practitioner.

Changes in Laboratory Values During Treatment

Response to leuprolide acetate, should be monitored by measuring serum levels of testosterone as well as prostate-specific antigen and prostatic 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 were maintained for as long as the patients received their injections. Transient increases in acid phosphatase levels have occurred early in treatment. However, by the fourth week, the elevated levels usually decrease to values at or near baseline.
During clinical trials isolated elevations of SGOT (ALT) were observed. In clinical trials leuprolide acetate was associated with elevation of total cholesterol, triglycerides, lactate dehydrogenase (LDH) and phosphorous and decreases in high-density lipoprotein (HDL) and white blood cell (WBC) counts.

Impairment of fertility

Studies in adults with leuprolide acetate have shown 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. 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 3,75 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, macrolide antibiotics, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Medicine/Laboratory Test Interactions

Diagnostic tests of pituitary gonadotropic and gonadal function conducted during treatment and up to 4 to 8 weeks after discontinuation of PRINOLID 3,75 therapy may be misleading, as therapeutic doses of PRINOLID 3,75 result in suppression of the pituitary-gonadal system.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When used monthly at the recommended dose, PRINOLID 3,75 usually inhibits ovulation and stops menstruation. However, contraception is not ensured by taking PRINOLID 3,75 and therefore patients should use non-hormonal methods of contraception during treatment. Patients should be advised that if they miss successive doses of PRINOLID 3,75, 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 3,75 is contraindicated during pregnancy (see section 4.3).
The safe use of PRINOLID 3,75 in pregnancy has not been established clinically.
Studies in animals have shown reproductive toxicity (see section 5.3). Before starting treatment with PRINOLID 3,75, pregnancy must be excluded. There have been reports of foetal malformation when PRINOLID 3,75 has been given during pregnancy.

Breastfeeding

PRINOLID 3,75 should not be used in women who are breastfeeding (see section 4.3) and mothers on PRINOLID 3,75 should be advised not to breastfeed their infants.

In girls with central precocious puberty: see section 4.3.

4.7 Effects on ability to drive and use machines

PRINOLID 3,75 may have adverse events that impair the patient's ability to drive or to use machinery due to visual disturbances and dizziness.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions seen with PRINOLID 3,75 are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

Men

In the majority of patients testosterone levels increase above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.
In cases where a "tumour flare" occurs after PRINOLID 3,75 therapy, an exacerbation may occur in any symptoms or signs due to disease which subside on continuation of therapy.
Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paraesthesia of the lower limbs or worsening of urinary symptoms (see section 4.4).

Women

Those adverse events occurring most frequently with PRINOLID 3,75 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).

Children

In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

b. Tabulated summary of adverse reactions

Men

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Infections and infestations	Less frequent	Rhinitis, fungal skin infection.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	Prostate tumor flare, aggravation of prostate cancer.
	Less frequent	Neoplasm.
Metabolism and nutrition disorders	Frequent	Anorexia / decreased appetite, weight fluctuation (gain / loss).
	Less frequent	Hyperglycaemia, abnormal weight gain
Psychiatric disorders	Frequent	Loss or decreased libido, increased libido, insomnia, depression (see section 4.4), mood changes (long-term use)*
	Less frequent	Mood changes (short-term use)*, sleep disorders.

Nervous system disorders	Frequent	Headache (occasionally severe).
	Less frequent	Dizziness, paraesthesia, pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma, somnolence.
Eye disorders	Less frequent	Amblyopia.
Ear and labyrinth disorders	Less frequent	Ear pain, tinnitus.
Cardiac disorders	Less frequent	Dysrhythmia, angina pectoris, ventricular extrasystoles.
Vascular disorders	Frequent	Hot flush, vasodilation, hypotension (see section 4.4), orthostatic hypotension.
	Less frequent	Angiopathy, hypertension, poor peripheral circulation.
Respiratory, thoracic and	Frequent	Dyspnoea.

mediastinal disorders	Less frequent	Epistaxis, haemoptysis, emphysema.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea.
Hepatobiliary disorders	Frequent	Hepatic function abnormal, liver function test abnormal (usually transient).
Skin and subcutaneous tissue disorders	Frequent	Dry skin, hyperhidrosis, rash, pruritis, urticaria, hair growth abnormal, hair disorder, night sweats, hypotrichosis, pigmentation disorder, cold sweat, hirsutism.
	Less frequent	Alopecia, rash, rash maculo-papular.
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle weakness, bone pain.
	Less frequent	Myalgia, weakness of lower extremities, pain in extremity.
Renal and urinary disorders	Less frequent	Dysuria, pollakiuria, haematuria, urinary retention, polyuria.
Reproductive system and breast disorders	Frequent	Breast tenderness, breast enlargement, breast pain, erectile dysfunction, gynaecomastia, libido decreased, penile swelling, penis disorder, prostate pain, testicular atrophy, testicular pain.
General disorders	Frequent	Fatigue, pain, injection site

and administration site conditions		reaction (e.g., induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis), peripheral oedema, mucosal dryness.
	Less frequent	Chest pain, asthenia, injection site irritation and inflammation, chills
Investigations	Frequent	Blood lactic dehydrogenase increased, PSA increased, bone density decreased, aspartate aminotransferase increased/AST, blood alkaline phosphatase increased.
	Less frequent	Haemoglobin decreased, blood urea increased, blood uric acid increased, blood calcium increased, alanine aminotransferase increased / ALT, gamma-glutamyltransferase increased, platelet count decreased, protein urine present, white blood cell count increased, reticulocyte count increased.
Long exposure (6 to 12 months)	Frequent	Diabetes mellitus, glucose tolerance impaired, total cholesterol increased, LDL increased, triglycerides increased, osteoporosis.

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

Women

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS

Metabolism and nutrition disorders	Frequent	Weight gain, weight loss.
	Less frequent	Decreased appetite, lipids abnormal.
Psychiatric disorders	Frequent	Insomnia, loss or decreased libido, increased libido, affect lability, mood altered, depression (see section 4.4).
Nervous system disorders	Frequent	Headache (occasionally severe), parasthesiae, dizziness.
	Less frequent	Pituitary haemorrhage has been reported following initial administration in patients with pituitary adenoma.
Eye disorders	Less frequent	Visual impairment.
Cardiac disorders	Less frequent	Palpitations.
Vascular disorders	Frequent	Hot flush, hypotension (see section 4.4), vasodilatation.
Gastrointestinal disorders	Frequent	Nausea.
	Less frequent	Diarrhoea, vomiting.
Hepatobiliary disorders	Less frequent	Liver function test abnormal (usually transient).

Skin and subcutaneous tissue disorders	Frequent	Acne, seborrhoea, dry skin, urticaria, skin odour abnormal, hyperhydrosis, hair growth abnormal, hirsutism, hair disorder, eczema, nail disorder, night sweats.
	Less frequent	Hair loss.
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, muscle weakness.
	Less frequent	Myalgia.
Reproductive system and breast disorders	Frequent	Vaginal haemorrhage, dysmenorrhoea, menstrual disorder, breast enlargement, breast engorgement, breast atrophy, genital discharge, vaginal discharge, galactorrhea, breast pain/tenderness, metrorrhagia, menopausal symptoms, dyspareunia, uterine disorder, vulvovaginitis, menorrhagia, vulvovaginal dryness.
General disorders and administration site conditions	Frequent	Feeling hot, irritability, oedema peripheral, injection site reaction (e.g. injection site induration, erythema, pain, abscesses, swelling, nodules, ulcers and necrosis)
	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.

Endometriosis

The following adverse events are associated with PRINOLID 3,75 in the management of 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.
Nervous system disorders *continue*	Less frequent	Somnolence, amnesia, syncope, ataxia.
Eye disorders	Frequent	Visual impairment, amblyopia.
	Less frequent	Eye disorder, eye pain.
Ear and labyrinth	Frequent	Vertigo

disorders		
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, 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.
Renal and urinary disorders	Frequent	Dysuria.
	Less frequent	Urinary incontinence, pollakiuria

Reproductive system and breast disorders	Frequent	Vulvovaginitis, 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.

Breast cancer

The following adverse events are associated with PRINOLID 3,75 in the management of breast cancer:

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestation	Frequent	Urinary tract infection, nasopharyngitis.
	Less frequent	Upper respiratory tract infection.
Blood and lymphatic system disorders	Frequent	Iron deficiency anaemia.
	Less frequent	Leukopenia.
Metabolism and nutrition disorders	Frequent	Appetite increased, abnormal weight gain, abnormal loss of weight, appetite decreased.
	Less frequent	Anorexia.
Psychiatric	Frequent	Depression, insomnia, nervousness, mood swings,

disorders		sleep disorder, affect lability, anxiety.
Nervous system disorders	Frequent	Headache, dizziness, dizziness postural, paraesthesia, somnolence, tremor, convulsions local.
Eye disorders	Frequent	Vision blurred, conjunctivitis.
Ear and labyrinth disorders	Frequent	Tinnitus.
Cardiac disorders	Frequent	Palpitations.
Vascular disorders	Frequent	Hot flushes.
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis, dyspnoea, cough, oropharyngeal pain.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, constipation, abdominal pain (upper/lower), stomatitis, retching, abdominal discomfort, tongue disorder.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, erythema, alopecia, acne, urticaria, night sweats, pigmentation disorder.
Musculoskeletal and connective tissue disorders	Frequent	Back pain, arthralgia, bone pain, neck pain, muscular weakness, musculoskeletal stiffness, periarthritis.
Renal and urinary	Frequent	Pollakiuria, nocturia.

disorders		
Reproductive system and breast disorders	Frequent	Dysmenorrhoea, metrorrhagia, menopausal symptoms, vulvovaginitis, menorrhagia.
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, injection site haemorrhage, irritability, malaise.
Investigations	Less frequent	Body temperature increased.

In women with early breast cancer treated with a GnRH agonist in combination with tamoxifen or an aromatase inhibitor, the most frequently observed adverse reactions included hot flush, musculoskeletal disorders, fatigue, insomnia, hyperhidrosis, vulvovaginal dryness and depression.

Children

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestation	Less frequent	Infection, rhinitis, influenza, pharyngitis, sinusitis.
Neoplasms benign, malignant and unspecified (including	Less frequent	Cervix neoplasm.

cysts and polyps)		
Immune system disorders	Less frequent	Hypersensitivity (fever, rash, e.g. itching, anaphylactic reactions).
Endocrine disorders	Less frequent	Precocious puberty, goiter.
Metabolism and nutrition disorders	Frequent	Growth retardation, abnormal weight gain.
	Less frequent	Increased appetite.
Psychiatric disorders	Frequent	Emotional lability
	Less frequent	Nervousness, depression.
Nervous system disorders	Frequent	Headache.
	Less frequent	Somnolence, syncope, hyperkinesia, pituitary haemorrhage following initial administration in patients with pituitary adenoma.
Cardiac disorders	Less frequent	Bradycardia.
Vascular disorders	Frequent	Vasodilatation.
	Less frequent	Hypertension, peripheral vascular disorder.
Respiratory, thoracic and mediastinal disorders	Less frequent	Epistaxis, asthma.
Gastrointestinal disorders	Frequent	Abdominal pain / abdominal cramps, nausea/vomiting
	Less frequent	Constipation, dysphagia, gingivitis, dyspepsia.
Skin and subcutaneous tissue disorders	Frequent	Rash including erythema multiforme, acne /seborrhoea, skin odour abnormal.
	Less frequent	Alopecia, hirsutism, hair disorder, nail disorder,

		leukoderma, skin hypertrophy, purpura.
Musculoskeletal and connective tissue disorders	Less frequent	Myalgia, arthropathy, myopathy, arthralgia.
Renal and urinary disorders	Less frequent	Urinary incontinence.
Reproductive system and breast disorders	Frequent	Vaginal haemorrhage, spotting**, vaginal discharge, vulvovaginitis, gynaecomastia.
	Less frequent	Cervix disorder, dysmenorrhoea, menstrual disorders, breast enlargement, breast pain, acquired feminisation.
General disorders and administration site conditions	Frequent	Pain, injection site reactions including abscess.
	Less frequent	Peripheral oedema, pyrexia, hypertrophy, conditions aggravated.
Investigations	Less frequent	Antinuclear antibody positive, red blood cell sedimentation rate increased.

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment) should be assessed as a sign of potential underdosage. The pituitary suppression should then be determined by an LHRH test.

Post-marketing experience

Post-marketing adverse events seen in Prostate Cancer, Endometriosis, Breast Cancer and Central Precocious Puberty are listed below and is of unknown frequency.

SYSTEM ORGAN	ADVERSE REACTIONS

CLASS	
Infections and infestations	Infection, urinary tract infection, pharyngitis, pneumonia.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Skin cancer.
Blood and lymphatic system disorders	Anaemia (reported for medicines of this class), [b, c] thrombocytopaenia, [b, c] leucopenia. [b, c]
Immune system disorders	Hypersensitivity reactions (including rash, pruritus, urticaria and rarely, wheezing or interstitial pneumonitis, anaphylactic reactions). [b, c]
Endocrine disorders	Goiter, pituitary apoplexy.
Metabolism and nutrition disorders	Diabetes mellitus, increased appetite, hypoglycaemia, dehydration, hyperlipidaemia/abnormal lipids, hyperphosphataemia, hypoproteinaemia, glucose tolerance / tolerance abnormal which may affect diabetic control.
Psychiatric disorders	Mood swings[a,] nervousness, libido increased, insomnia, sleep disorder, depression[a,] anxiety, delusion, suicidal ideation and attempt [b, c]

Nervous system disorders	Dizziness, headache, paraesthesia, lethargy, memory impairment, dysgeusia, hypoaesthesia, syncope, neuropathy peripheral, cerebrovascular accident, loss of consciousness, transient ischemic attack, [b, c] paralysis, neuromyopathy, convulsion.
Eye disorders	Vision blurred, eye disorder, visual impairment, amblyopia, dry eye.
Ear and labyrinth disorders	Tinnitus, hearing impaired.
Cardiac disorders	Cardiac failure congestive, [b, c] dysrhythmia, myocardial infarction [b, c], angina pectoris [b, c], tachycardia, bradycardia, sudden cardiac death [b], palpitations [b], electrocardiogram QT prolonged [b].
Vascular disorders	Hot flushes [d], lymphoedema, hypertension, phlebitis [b, c], thrombosis, flushing [d], hypotension, varicose vein. [b, c]
Respiratory, thoracic and mediastinal disorders	Pleural rub [b, c], pulmonary fibrosis [b, c], epistaxis, dyspnoea, haemoptysis [b, c], cough, pleural effusion [b, c], lung infiltration [b, c], respiratory disorder, sinus congestion, pulmonary embolism [b, c], interstitial lung disease.
Gastrointestinal disorders	Constipation, nausea, vomiting, gastro-intestinal haemorrhage, abdominal distention, abdominal pain [d], diarrhoea, dysphagia, dry mouth, duodenal ulcer [b, c], gastrointestinal disorder, peptic ulcer, rectal polyp [b, c].
Hepatobiliary disorders [b, c]	Hepatic function abnormal [b, c], serious liver injury [b, c], jaundice [b, c].

Skin and subcutaneous tissue disorders	Alopecia, ecchymosis, rash, dry skin, photosensitivity reaction, urticaria, dermatitis, hair growth abnormal, pruritus, pigmentation disorder, skin lesion, hyperhidrosis [d].
Musculoskeletal and connective tissue disorders	Myalgia, bone swelling, arthropathy, arthralgia, ankylosing spondylitis [b, c], tenosynovitis, spinal fracture [b, c], reduction in bone mass which may occur with the use of GnRH agonists [b, c].
Renal and urinary disorders	Urinary incontinence, pollakiuria, micturition urgency, haematuria, bladder spasm [b, c], urinary tract disorder [b, c], urinary tract obstruction [b, c].
Reproductive system and breast disorders	Gynaecomastia [b, d], breast tenderness, vaginal haemorrhage [c, d], testicular atrophy [b, d], testicular pain [b], breast pain, testicular disorder [b, d], menstrual disorder [c, d], penile swelling [b], penis disorder [b], prostatic pain [b, d], metrorrhagia [c, d].
General disorders and administration site conditions	Pain, chest pain [d], 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, weight increased [d], inflammation [c, d], pelvic fibrosis [c, d].
Investigations	Blood urea increased, increased blood uric acid, blood creatinine increased, blood calcium increased [b, c], abnormal electrocardiogram [b, c], ECG signs of myocardial ischaemia [b, c], decreased platelet count [b, c], abnormal liver function test, decreased blood potassium [b, c], increased white blood cell count, decreased white blood cell count [b, c], prolonged prothrombin time [b, c], prolonged activated partial thromboplastin time [b, c], cardiac murmur, increased low

	density lipoprotein [b, c], increased blood triglycerides [b, c], increased blood bilirubin [b, c].

[a] Depression and mood swing are commonly observed adverse reactions with long term use of GnRH agonists.

[b] Only in men/prostate cancer population

[c] Only in women/endometriosis and breast cancer populations

[d] Only in children/CPP population

c. Description of selected adverse reactions

Women

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischaemic attack. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH agonist and these events.

Changes in Bone Density

In controlled studies, patients with endometriosis (six months of therapy) were treated with leuprolide acetate (as in PRINOLID 3,75). 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.

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 cases of overdose has been reported.

In overdose, side effects would be exacerbated and exaggerated (see sections 4.4 and 4.8).

In cases of overdosage, the patients should be monitored closely, and treatment should be symptomatic and supportive.

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), which

possesses greater potency than the natural hormone.

Mechanism of action

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin. 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.

Paediatric population

In children with central precocious puberty (CPP), stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females, respectively. Reduction of gonadotropins will allow for normal growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate.

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

A single administration of leuprolide acetate depot suspension in prostatic carcinoma patients, at a dose of 3,75 mg by subcutaneous and intramuscular routes, provided mean leuprolide acetate plasma concentrations of 0,7 ng/mL at the end of one month. There was no indication of any medicine accumulation.

Serum levels of leuprolide acetate 3,75 mg were measured in 11 patients with pre-menopausal breast cancer over 12 weeks. Mean leuprolide acetate levels were above 0,1

ng/mL after four weeks and remained stable after re-injection (at 8 and 12 weeks). There was no tendency for medicine accumulation.

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 %.

Metabolism

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 ^{14}C-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.

Excretion

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.

Paediatric Patients

In a study of 22 children with central precocious puberty, doses of leuprolide acetate depot suspension were given every four weeks and plasma levels were determined according to weight categories as summarised below.

Patient Weight Range (kg)	**Group Weight Average (kg)**	**Dose (mg)**	**Trough Plasma Leuprolide Level mean ± SD (ng/mL)***
20,2 – 27,0	22,7	7,5	0,77 ± 0,33
28,4 – 36,8	32,5	11,25	1,25 ± 1,06
39,3 – 57,5	44,2	15,0	1,59 ± 0,65

* Group average values determined at Week 4 immediately prior to leuprolide injection.

Medicine levels at 12 and 24 weeks were similar to respective 4-week levels.

5.3 Preclinical safety data

A teratogenic effect has been observed in rabbits but not in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilised powder

Gelatin

Mannitol

Poly(lacticglycolic) acid 75:25

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 3,75 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 glass ampoule containing solvent; 1 disposable syringe and two 22 G 1½ needles.

Solvent

2 ml colourless glass ampoule, with yellow identification ring and white cutting ring.

6.6 Special precautions for disposal

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

Preparation of administration

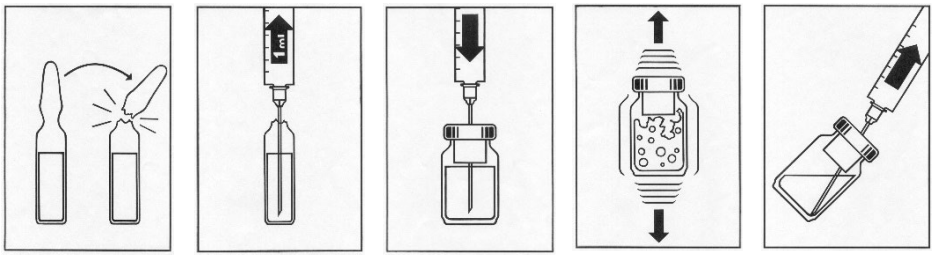
PRINOLID 3,75 should reconstituted and administered monthly as a single intramuscular or subcutaneous injection in accordance with the following directions:

1. Press to open the ampoule's neck. (A)
2. Using the syringe with a 22-gauge needle provided, withdraw 1 mℓ of diluent from the ampoule. (B)

   Extra diluent is provided, and any remaining diluent should be discarded.
3. Remove the cover of the vial and inject the diluent into the vial. (C)
4. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky. (D)

5. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

No other fluid should be used for reconstitution of PRINOLID 3,75.



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)

55/21.10/0733

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT