

Shopen Pharmaceuticals Ltd.

LUCRIN DEPOT® 11.25 mg - Dimensions: 130X645 - FRONT - Date: 1.3.2000

PHYSICIAN PRESCRIBING INFORMATION

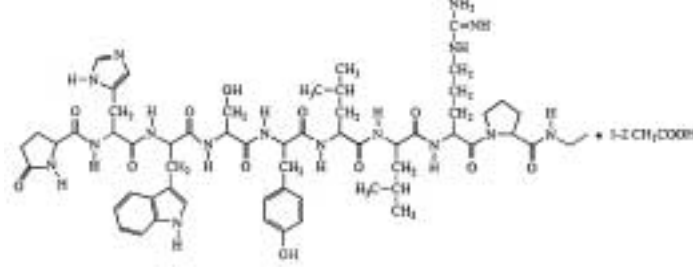
LUCRIN DEPOT® 11.25 mg

Leuprolide Acetate for Depot Suspension (11.25 mg)

DESCRIPTION

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

The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) and the structural formula is as follows:



Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) is a formulation of leuprolide acetate supplied in a vial containing sterile lyophilized microspheres. When mixed with diluent, it becomes a suspension which is administered as an intramuscular or subcutaneous injection every three months.

Active/Inactive Ingredients

The single-dose vial of Leuprolide Acetate Depot Suspension 3-Month (11.25 mg) contains leuprolide acetate (11.25 mg), a polymer, poly (DL-lactic acid) 99.3 mg and D-mannitol 19.45 mg.

The compound is easily soluble in polar solutions such as water and anhydrous ethanol and propylene glycol. It is nearly insoluble in chloroform. The pH value of a solution containing 100 mg dry powder of leuprolide acetate in one mL of solution is approximately 5 to 7.

The accompanying ampule of diluent used for reconstitution with the leuprolide acetate powder contains a clear, colorless, slightly viscous solution of carboxymethylcellulose (10 mg), D-mannitol (100 mg), polysorbate 80 (2 mg), water for injection (2 ml) and glacial acetic acid to control pH.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 steroidogenesis. This effect is reversible on discontinuation of therapy.

Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Nobel and Dunning male rats and DMBA-induced mammary tumors in female rats), as well as atrophy of the reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone 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 drug therapy at recommended doses.

Pharmacokinetics

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

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 4, a mean leuprolide plasma concentration of .26 (± .10) ng/mL was noted. It then declined to a mean leuprolide plasma concentration of 0.17 (± .08) ng/mL at 12 weeks.

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 ¹⁴C-labeled leuprolide was metabolized into smaller inactive peptides which may be further catabolized.

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 drug 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.

The pharmacokinetics of the drug in hepatic- and renal-impaired patients have not been determined.

INDICATIONS

Prostate Cancer

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) is indicated in the palliative treatment of advanced prostatic cancer.

Endometriosis

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) 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

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) 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.

CONTRAINDICATIONS

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) is contraindicated in patients with known hypersensitivity to leuprolide acetate, similar nonapeptides, or any of the excipients.

Isolated cases of anaphylaxis have been reported with the monthly formulation of Leuprolide Acetate for Depot Suspension.

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) is not suitable for the treatment of patients following an orchiectomy.

Undiagnosed abnormal vaginal bleeding.

Leuprolide Acetate for Depot Suspension is contraindicated in women who are or may become pregnant while receiving the drug. Leuprolide Acetate for Depot Suspension may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of Leuprolide Acetate for Depot Suspension throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

Use in women who are breastfeeding.

WARNINGS

Prostate Cancer

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with GnRH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily leuprolide acetate injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

Endometriosis/Uterine Fibroids

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy at adequate doses.

PRECAUTIONS

As the effects of Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) are present throughout the course of therapy, the drug should only be used in patients who require hormonal suppression for at least three months.

Prostate Cancer

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see WARNINGS).

Laboratory Tests

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 of treatment. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections on time. Transient increases in acid phosphatase levels sometimes occurred early in treatment. However, by the fourth week, the elevated levels usually decrease to values at or near baseline.

Contraception

When used at the recommended dose and dosing interval, Leuprolide Acetate for Depot Suspension usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking Leuprolide Acetate for Depot Suspension. Therefore patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus (see CONTRAINDICATIONS).

Endometriosis/Uterine Fibroids

Since bone loss can be anticipated as part of natural menopause, it may also be expected to occur during a medically-induced hypoestrogenic state. Bone loss has been found to be reversible after completion of a six month course of leuprolide acetate. Experience with Leuprolide Acetate for Depot Suspension in females has been limited to women 18 years of age and older, treated for 6 months.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with Leuprolide Acetate Depot Suspension. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy

Leuprolide Acetate for Depot Suspension is contraindicated in women who are or may become pregnant while receiving the drug (see CONTRAINDICATIONS).

Nursing Mothers

It is not known whether leuprolide acetate is excreted in human milk. Therefore, it should not be administered to a nursing mother (see CONTRAINDICATIONS).

ADVERSE REACTIONS

Prostate Cancer

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

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 paresthesia of the lower limbs or worsening of urinary symptoms (see WARNINGS).

Table 1 summarizes the results of an open-labeled comparative study that was conducted to determine the efficacy, safety and tolerability of leuprolide acetate one-month and three-month depot suspension. The adverse events reported are as follows:

Table 1
MOST COMMON ADVERSE EVENTS*
(Intention To Treat Analysis)

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg)	1 Month Group N=80	1 Month Group (%)	3 Month Group N=157	3 Month Group (%)
Gastrointestinal System				
Increased weight	20	25.0	41	26.1
Anorexia	9	11.3	20	12.7
Endocrine System				
Hot flashes	52	65.0	81	51.6
Decreased libido	42	52.5	87	55.4
Increased sweating	38	47.5	66	42.0
Urogenital System				
Nocturia	43	53.8	88	56.1
Impotence	41	51.3	84	53.5
Dysuria	19	23.8	38	24.2
Testis disorder	24	30.0	33	21
Urinary tract infection	13	16.3	14	8.9
PSA increase	9	11.3	12	7.6
Integumentary System				
Local reaction at injection site	8	10.0	22	14
Pruritus	14	17.5	7	4.5
Musculoskeletal System				
Skeletal pain	22	27.5	34	21.7
Miscellaneous				
Fatigue	18	22.5	31	19.7
Muscle weakness	17	21.3	23	14.6

* Adverse events mentioned at least once by more than 10% of patients in either of the two treatment groups

Endometriosis and Uterine Fibroids

The monthly formulation of Leuprolide Depot 3.75 mg was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in ≥ 5% of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

Table 2
Adverse Events Reported to be Causally Related to Drug in ≥ 5% of Patients

	Endometriosis (2 Studies)		Uterine Fibroids (4 Studies)	
	Leuprolide Depot 3.75 mg N=166 N (%)	Placebo N=31 N (%)	Leuprolide Depot 3.75 mg N=166 N (%)	Placebo N=163 N (%)
Body as a Whole				
Asthenia	5 (3)	0 (0)	14 (8.4)	8 (4.9)
General pain	31 (19)	1 (3)	14 (8.4)	10 (6.1)
Headache *	53 (32)	2 (6)	43 (25.9)	29 (17.8)
Cardiovascular System				
Hot flashes/sweats *	139 (84)	9 (29)	121 (72.9)	29 (17.8)
Gastrointestinal System				
Nausea/vomiting	21 (13)	1 (3)	8 (4.8)	6 (3.7)
GI disturbances *	11 (7)	1 (3)	5 (3.0)	2 (1.2)
Metabolic and Nutritional Disorders				
Edema	12 (7)	1 (3)	9 (5.4)	2 (1.2)
Weight gain/loss	22 (13)	0 (0)	5 (3.0)	2 (1.2)
Endocrine System				
Acne	17 (10)	0 (0)	0 (0)	0 (0)
Hirsutism	2 (1)	1 (3)	1 (0.6)	0 (0)
Musculoskeletal System				
Joint disorder *	14 (8)	0 (0)	13 (7.8)	5 (3.1)
Myalgia *	1 (1)	0 (0)	1 (0.6)	0 (0)
Nervous System				
Decreased libido *	19 (11)	0 (0)	3 (1.8)	0 (0)
Depression/emotional lability *	36 (22)	1 (3)	18 (10.8)	7 (4.3)
Dizziness	19 (11)	0 (0)	3 (1.8)	6 (3.7)
Nervousness *	8 (5)	0 (0)	8 (4.8)	1 (0.6)
Neuromuscular disorders *	11 (7)	0 (0)	3 (1.8)	0 (0)
Paresthesias	12 (7)	0 (0)	2 (1.2)	1 (0.6)
Skin and Appendages				
Skin reactions	17 (10)	1 (3)	5 (3)	2 (1.2)
Urogenital System				
Breast changes/tenderness/pain *	10 (6)	0 (0)	3 (1.8)	7 (4.3)
Vaginitis *	46 (28)	0 (0)	19 (11.4)	3 (1.8)

In these same studies, symptoms reported in < 5% of patients included: Body as a Whole - Body odor, Flu syndrome, Injection site reactions; Cardiovascular System - Palpitations, Syncope, Tachycardia; Digestive System - Appetite changes, Dry mouth, Thirst; Endocrine System - Androgen-like effects; Hemic and Lymphatic Systems - Ecchymosis, Lymphadenopathy; Nervous System - Anxiety,* Insomnia/Sleep disorders,* Delusions, Memory disorder, Personality disorder; Respiratory System - Rhinitis; Skin and Appendages - Alopecia, Hair disorder, Nail disorder; Special Senses - Conjunctivitis, Ophthalmologic disorders,* Taste perversion; Urogenital System - Dysuria,* Lactation, Menstrual disorders.

* = Physiologic effect of the drug.

In one controlled clinical trial utilizing the monthly formulation of Leuprolide Depot, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of Leuprolide Depot. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included glossitis, hypesthesia, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In a pharmacokinetic trial involving 20 healthy female subjects receiving Leuprolide Depot 3-Month 11.25 mg, a few adverse events were reported with this formulation that were not reported previously. These included face edema, agitation, laryngitis, and ear pain.

Changes in Bone Density

In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with Leuprolide Depot 3.75 mg. 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 pretreatment value. For those patients who were tested at six or twelve months after discontinuation of therapy, mean bone density returned to within 2% of pretreatment. When Leuprolide Depot 3.75 mg 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.

Changes in Laboratory Values During Treatment

Liver Enzymes

Three percent of uterine fibroid patients treated with Leuprolide Depot 3.75 mg, manifested posttreatment 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 12% of the endometriosis patients who received Leuprolide Depot 3.75 mg and in 32% of the subjects receiving Leuprolide Depot 3-Month 11.25 mg.

Of those endometriosis and uterine fibroid patients whose pretreatment 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 pretreatment values were statistically significant (p<0.03).

There was essentially no increase in the LDL/HDL ratio in patients from either population receiving Leuprolide Depot 3.75 mg.

Post-marketing Surveillance

The following adverse events have been observed with this or other formulations of leuprolide acetate injection. As leuprolide has multiple indications, and therefore patient populations, some of these adverse events may not be applicable to every patient. For a majority of these adverse events, a cause and effect relationship has not been established.

Body as a whole: abdomen enlarged, asthenia, chills, fever, general pain, headache, infection, inflammation, photosensitivity reactions, swelling (temporal bone); Cardiovascular: angina, bradycardia, cardiac arrhythmia, congestive heart failure, ECG changes/ischemia, hypertension, hypotension, murmur, myocardial infarction, phlebitis, pulmonary emboli, stroke, syncope/blackouts, thrombosis, transient ischemic attack, varicose veins; Digestive: constipation, diarrhea, dry mouth, duodenal ulcer, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, hepatic dysfunction, increased appetite, liver function tests abnormal, nausea, peptic ulcer, rectal polyps, thirst, vomiting; Endocrine: diabetes, thyroid enlargement; Hemis/Lymphic: anemia, ecchymosis, lymphedema, PT increased, PTT increased, platelets decreased, WBC decreased, WBC increased; Metabolic and Nutritional: BUN increased, calcium increased, creatinine increased, dehydration, edema, hyperlipidemia (total cholesterol, LDL - cholesterol, triglycerides), hyperphosphatemia, hypoglycemia, hypoproteinemia, potassium decreased, uric acid increased; Musculoskeletal: ankylosing spondylosis, joint disorders, joint pain, myalgia, pelvic fibrosis, spinal fracture, paralysis, tenosynovitis-like symptoms; Nervous: anxiety, delusions, depression, dizziness, hypesthesia, insomnia, lethargy, libido increased, lightheadedness, memory disorder, mood swings, nervousness, neuromuscular disorders, numbness, paresthesia, peripheral neuropathy, sleep disorders; Respiratory: cough, dyspnea, epistaxis, hemoptysis, pharyngitis, pleural effusion, pleural rub, pneumonia, pulmonary fibrosis, pulmonary infiltrate, respiratory disorders, sinus congestion; Skin and Appendages: carcinoma of skin/ear, dermatitis, dry skin, hair growth, hair loss, hard nodule in throat, pigmentation, pruritus, rash, skin lesions, urticaria; Special Senses: abnormal vision, amblyopia, blurred vision, dry eyes, hearing disorder, ophthalmologic disorders, taste disorders, tinnitus; Urogenital: bladder spasms, breast pain, breast tenderness, gynecomastia, hematuria, incontinence, menstrual disorders, penile swelling, penis disorders, prostate pain, testicular atrophy, testicular pain, testicular size decreased, urinary disorders, urinary frequency, urinary obstruction, urinary tract infection, urinary urgency.

Isolated cases of anaphylaxis have been reported.

Injection site reactions including pain, inflammation, sterile abscess, induration, and hematoma have been reported.

There have been very rare reports of suicidal ideation and attempt.

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose of leuprolide acetate depot suspension. In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnea, decreased activity and local irritation at the injection site. In cases of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

General

Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) must be administered under the supervision of a physician.

The recommended dose of Leuprolide Acetate for Depot Suspension 3-Month (11.25 mg) is 11.25 mg, administered as a single subcutaneous or intramuscular injection every three months.

As with other drugs administered by injection, the injection sites should be varied periodically.

For use in treatment of endometriosis

It is recommended that therapy begin with the first day of the menstrual cycle after pregnancy has been ruled out. Development of amenorrhea is usually evidence of a clinical response, although spotting or bleeding from the atrophic endometrium can still occur.

For use in treatment of uterine fibroids

Recommended duration of therapy is up to 6 months.

Reconstitution

The vial of leuprolide acetate depot suspension 3-month (11.25 mg) should be reconstituted immediately prior to administration and administered every three months as a single subcutaneous or intramuscular injection in accordance with the following directions:

- Using a syringe with a 23 gauge needle, withdraw two mL of diluent from the ampule, and inject it into the vial of leuprolide acetate depot suspension using aseptic technique.
- Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
- Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the solution has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

No other fluid should be used for reconstitution of leuprolide acetate depot suspension 3-month (11.25 mg) powder.

STORAGE

The shelf life for this product is 36 months unopened. No refrigeration is necessary, store at room temperature. Do not store above 30°C. Once reconstituted with the sterile diluent, the suspension should be administered immediately. However, the suspension is considered stable for up to 24 hours at 25°C. Protect from light.

HOW SUPPLIED

Leuprolide Acetate Depot Suspension 3-Month (11.25 mg) is available in a single dose administration kit. Each kit contains one vial of sterile lyophilized microspheres of leuprolide acetate with gaseous and two alcohol wipes.

LIST NUMBERS

List Number(s)	Products
M346	Leuprolide Acetate for Depot Suspension 11.25 mg Vial
M357	Single-Dose Administration Kit
G755	2 mL Diluent Ampule

Manufacturer: Takeda - Japan; For Abbott Labs - Spain

Importer: Promedico Ltd., 4 Baltimore St., Petach-Tikva

PRO-LUCI-02 (02/00)

