DEPO-PROVERA® 500

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Depo-Provera® 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Depot-medroxyprogesterone acetate injectable suspension is available as 500 mg/3.3 ml vial.

Excipients with known effect:

Methyl paraben
Propyl paraben
Sodium chloride
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for intramuscular injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEPO-PROVERA® 500 is indicated for: Palliation of inoperable recurrent or metastatic carcinoma of endometrium, breast, ovary and kidney.

4.2 Posology and method of administration

Posology

Injectable suspensions should be shaken well before use.

The site of injection should be cleansed using standard methods prior to administration of the injection.

Recurrent and/or Metastatic Breast Cancer

Injectable DMPA initial dose 500 to 1000 mg intramuscularly per day for 28 days. The patient should then be placed on a maintenance schedule of 500 mg twice weekly as long as she responds to treatment.

Recurrent and/or Metastatic Endometrial or Renal Cancer

Injectable DMPA 400 to 1000 mg intramuscularly per week is recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month.

Long-Term Use

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DMPA injection long-term **(see Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties, *Clinical trials relating to bone mineral density*)**, a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Use in Children

DMPA IM is not indicated before menarche. Data are available in adolescent females (12-18 years) **(see Section 5.1 Pharmacodynamic properties, *Clinical trials, Changes in BMD in adolescent females (aged 12–18)*.** Other than concerns about loss of BMD, the safety and effectiveness of DMPA IM are expected to be the same as for postmenarcheal adolescent and adult females.

Hepatic Insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency (see Section 3.3 Contraindications).

Renal Insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

4.3 Contraindications

Depo-Provera® is contraindicated in the following situations:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- when pregnancy is suspected or confirmed;
- undiagnosed vaginal bleeding;
- severe liver impairment.

4.4 Special warnings and precautions for use

Any unexpected vaginal bleeding that takes place during treatment with Depo-Provera® should be investigated.

Depo-Provera® can cause fluid retention, and as a result, precaution is necessary in patients whose pre-existing clinical situation may be negatively affected by the retention of liquids.

Patients with a history of clinical treatment for mental depression should be carefully monitored when undergoing therapy with Depo-Provera®.

Reduced glucose tolerance has been observed in some patients receiving Depo-Provera®. For this reason, diabetics should be kept under careful observation during treatment.

When pathology examinations of endometrium or endocervix tissues are carried out, the pathologist should be advised that the patient is under treatment with Depo-Provera®.

The doctor and the laboratory should be aware that treatment with Depo-Provera® can reduce the levels of the following endocrine biomarkers:
- steroids in plasma and urine (e.g. cortisol, oestrogen, pregnanediol, progesterone, testosterone)
- gonadotrophins in plasma and urine [e.g. Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH)]
- female sex hormone binding globulins

Treatment with Depo-Provera® should not be resumed until the patient has been examined for unexpected occurrence of partial or complete loss of vision, proptosis, diplopia or migraines. If the examination reveals the existence of papilloedema or vascular lesions of the retina, the treatment should not be resumed.

Depo-Provera® has not been associated with the induction of thrombotic or thromboembolic disorders, but its use in patients with a prior history of venous thromboembolism (VTE) is not recommended. Discontinuation is also advised for patients who develop VTE during treatment with Depo-Provera®.

Loss of bone mineral density:

There are no studies on the effect caused by medroxyprogesterone, administered parenterally, on bone mineral density in oncological treatment.

It could be necessary to make an assessment of bone mineral density in patients who are undergoing prolonged treatment with Depo-Provera® (see Section 4.2 Long-Term Use).

Treatment with Depo-Provera® reduces serum levels of oestrogen and is associated with a statistically significant loss of bone mineral density, resulting from an adaptation of the bone metabolism to a lower level of oestrogen. Bone loss increases with prolonged treatment duration, and may be not completely reversible in some women. It is not known whether treatment of young women with Depo-Provera® during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for fractures in later life, i.e. after menopause.

A study to assess the BMD effects of Depo-Provera in adolescent females showed that its use was associated with a statistically significant decline in BMD from baseline.

After discontinuing depot medroxyprogesterone acetate intramuscular (DMPA-IM) in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine, 4.6 years at the total hip, and 4.6 years at the femoral neck (see Section 5.1). However, in some participants, BMD did not fully return to baseline during follow-up and the long-term outcome is not known in this group.

A large observational study of predominantly adult female contraceptive users showed that use of DMPA-IM did not increase risk for bone fractures. It should be noted that this study could not determine whether use of medroxyprogesterone acetate has an effect on fracture rate later in life (see Section 5.1 Clinical trials relating to bone mineral density).

It is recommended that all patients should have adequate ingestion of calcium and vitamin D.

Breast cancer

After various epidemiological studies, no increase in the risk of breast cancer was found in users of injectable prolonged-release progestogen, when compared to non-users. However, an increase was found in the relative risk (for example 2.0 in one study) in women who used prolonged-release injectable progestogen or had used it in previous years. From these data it is not possible to infer whether the increased rate of diagnoses of breast cancer in women who were users is due to an increase of vigilance, to the biological effects of injectable progestogen or to a combination of both reasons.

Prolonged anovulation, with amenorrhoea and/or an irregular menstrual pattern, can occur after the administration of a single dose or multiple administration of Depo-Provera®.

Depo-Provera® can give rise to Cushingoid symptoms.

Some patients in treatment with Depo-Provera® may present suppressed adrenal function. Depo-Provera® may reduce blood levels of corticotropin (ACTH) and hydrocortisone.

The doctor and the laboratory should be informed that in addition to the biomarkers referred to above, the use of Depo-Provera® in oncological indications can also cause partial adrenal insufficiency (reduction of the response of the adrenal-pituitary axis) during the metyrapone test. Therefore, capacity of the adrenal cortex to respond to corticotropin (ACTH) should be demonstrated before the administration of metyrapone.

This medicine contains methyl parahydroxybenzoate (methyl paraben) and propyl parahydroxybenzoate (propyl paraben). It can cause allergic reactions (possibly delayed), and, exceptionally, bronchial spasm.

This medicine contains sodium. It contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide, when administered concomitantly with high doses of Depo-Provera®, can significantly reduce serum levels of medroxyprogesterone acetate. The possibility of reducing the efficacy of high doses of Depo-Provera® should be taken into consideration when using aminoglutethimide simultaneously.

Medroxyprogesterone acetate (MPA) is metabolized *in vitro* primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects of CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy

Depo-Provera® is contraindicated during pregnancy.

Notifications suggest, in certain circumstances, an association between intrauterine exposure to progestogen medications during the first three months of pregnancy and the occurrence of genital anomalies in the foetus.

Children resulting from unintentional pregnancies that took place 1 to 2 months after administration of Depo-Provera® can present an increased risk of being born with low weight, which in turn is associated with an increased risk of neonatal death. The risk attributed is low since pregnancy during treatment with Depo-Provera® is infrequent. There is no definitive information on the other formulations of medroxyprogesterone acetate (see Section 5.2 Distribution).

If the pregnancy occurs during the therapy, the patient should be informed about the potential risks for the foetus.

Breastfeeding

Medroxyprogesterone acetate and its metabolites are excreted in breast milk. There is no evidence that this fact represents a risk to the infant (see Section 5.2 Distribution).

Fertility

Depo-Provera® has a prolonged contraceptive effect. In the event of conception, the average time for this to occur is after 10 months (ranging from 4-31 months) after the last administration, but there is no relation to the duration of the treatment.

4.7 Effects on ability to drive and use machines

Depo-Provera® may cause headaches and dizziness. Patients should be advised not to drive or operate machinery if affected.

4.8 Undesirable effects

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from 1337 patients who received medroxyprogesterone acetate in 4 pivotal studies that evaluated efficacy and safety of medroxyprogesterone acetate for oncology indications.

System Organ Class	Very Common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Frequency Not Known (cannot be estimated from the available data)
Immune system disorders			Angioedema	Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders			Corticoid-like effects		Prolonged anovulation
Metabolism and nutritional disorders		Weight fluctuation, Increased appetite	Diabetes mellitus exacerbated, Hypercalcaemia		
Psychiatric disorders		Insomnia	Depression, Euphoria, Changes in libido	Nervousness	Confusion
Nervous system disorders		Headache, Dizziness, Tremors		Cerebral infarction, Somnolence	Loss of concentration, Adrenergic-like effects
Eye disorders					Retinal embolism and thrombosis, Cataract diabetic, Visual impairment
Cardiac disorders			Cardiac failure congestive	Myocardial infarction	Tachycardia, Palpitations
Vascular disorders			Thrombo phlebitis	Embolism and thrombosis	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism		
Gastrointestinal disorders		Vomiting, Constipation, Nausea	Diarrhoea, Dry mouth		
Hepatobiliary disorders				Jaundice	
Skin and subcutaneous tissue disorders		Hyperhidrosis	Acne, Hirsutism	Alopecia, Rash	Lipodystrophy acquired*, Urticaria, Pruritus
Musculoskeletal and connective tissue disorders			Muscle spasms		
Renal and urinary system disorders					Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain		Amenorrhoea, Uterine cervical erosions, Cervical discharge, Galactorrhoea
General disorders and administration site conditions		Oedema/fluid retention, Fatigue, Injection site reaction*	Injection site pain/ tenderness*	Malaise, Pyrexia	Injection site persistent atrophy/ indentation/ dimpling*, Injection site nodule/lump*
Investigations				Glucose tolerance decreased, Blood pressure increased	Liver function test abnormal, White blood cell count increased, Platelet count increased

* Adverse drug reaction identified post-marketing

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

4.9 Overdose

Oral doses of up to 3 g per day have been well-tolerated.
Treatment for an overdose must be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Depo-Provera® 500, 150 mg/ml Suspension for injection
Pharmacotherapeutic group: 16.2.1.3 – Antineoplastic and immunomodulating agents. Hormones and anti-hormones. Hormones. Progestogens, ATC code: L02AB02

Mechanism of action

Medroxyprogesterone acetate is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been shown to have various pharmacological actions in the endocrine system:

- Inhibition of the gonadotrophins of the pituitary gland (FSH and LH).
- Reduction of blood levels of ACTH and hydrocortisone.
- Reduction of testosterone in circulation.
- Reduction in levels of oestrogen in circulation (resulting from inhibition of FSH together with enzymatic induction of hepatic reductase, which gives rise to increased clearance of testosterone and a consequent reduction of the conversion of androgens into oestrogens).

All these actions result in certain pharmacological events as described below.
Medroxyprogesterone acetate shows antitumour activity. Administration of medroxyprogesterone in high doses (both orally and by intramuscular injection) is effective in the palliative treatment of hormonal response in malignant neoplasms.

Clinical trials

Clinical trials relating to bone mineral density

Changes in BMD in adult women

In a controlled clinical study, adult women using DMPA-IM for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of treatment, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 below for further details.
After stopping use of DMPA-IM, BMD increased towards baseline values during the post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery.
In the same clinical study, a limited number of women who had used DMPA-IM for 5 years were followed-up for 2 years after stopping DMPA-IM use. BMD increased towards baseline values during the 2-year post-therapy period. Two years after stopping the treatment, mean BMD had increased at all 3 skeletal sites but deficits remained (see Table 1 below).

Table 1. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adults by Skeletal Site and Cohort after 5 Years of Therapy with DMPA-IM and after 2 Years Post-Therapy or 7 Years of Observation (Control)

Time in study	Spine		Total hip		Femoral neck	
	DMPA	Control	DMPA	Control	DMPA	Control
5 years*						
n	33	105	21	65	34	106
Mean	-5.4%	0.4%	-5.2%	0.2%	-6.1%	-0.3%
(SD)	(3.57)	(3.27)	(3.60)	(3.18)	(4.68)	(5.22)
95% CI	-6.65; -4.11	-0.20; 1.06	-6.80; -3.52	-0.60; 0.98	-7.75; -4.49	-1.27; 0.73
7 years**						
n	12	60	7	39	13	63
Mean	-3.1%	0.5%	-1.3%	0.9%	-5.4%	-0.1%
(SD)	(3.15)	(3.65)	(4.95)	(3.81)	(2.73)	(5.88)
95% CI	-5.13; -1.13	-0.39; 1.49	-5.92; 3.23	-0.29; 2.17	-7.03; -3.73	-1.51; 1.45

* The treatment group consisted of women who received DMPA-IM for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received DMPA-IM for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.
SD = Standard Deviation
CI = Confidence Interval

Changes in BMD in adolescent females (aged 12–18)

Results from an open-label, non-randomised, clinical study of DMPA-IM (150 mg IM every 12 weeks for up to 240 weeks (4.6 years), followed by post-treatment measurements) in adolescent females (12–18 years) also showed that DMPA-IM use was associated with a significant decline in BMD from baseline. Among subjects who received ≥4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1% after 240 weeks (4.6 years); mean decreases for the total hip and femoral neck were -6.4% and -5.4%, respectively. Please refer to Table 2.

In contrast, a non-comparable cohort of unmatched, untreated subjects, with different baseline bone parameters from the DMPA users, showed mean BMD increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively.

Table 2. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adolescents Receiving ≥4 Injections per 60-week Period, by Skeletal Site

Duration of treatment	DMPA-IM	
	N	Mean % change [95% CI]
Total hip BMD		
Week 60 (1.2 years)	113	-2.7 [-3.27; -2.12]
Week 120 (2.3 years)	73	-5.4 [-6.16; -4.64]
Week 180 (3.5 years)	45	-6.4 [-7.38; -5.37]
Week 240 (4.6 years)	28	-6.4 [-8.56; -4.24]
Femoral neck BMD		
Week 60	113	-2.9 [-3.72; -2.15]
Week 120	73	-5.3 [-6.23; -4.37]
Week 180	45	-6.0 [-7.31; -4.59]
Week 240	28	-5.4 [-7.81; -3.00]
Lumbar spine BMD		
Week 60	114	-2.5 [-2.95; -1.98]
Week 120	73	-2.7 [-3.57; -1.91]
Week 180	44	-2.7 [-3.99; -1.35]
Week 240	27	-2.1 [-4.16; -0.07]

CI = Confidence Interval

Post-treatment follow-up of adolescent participants from the same study, who received at least 1 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA-IM use is shown in Table 3. The median number of injections received in this cohort during the treatment phase was 9. At the time of the final DMPA injection, BMD % changes from baseline in this cohort were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time, these BMD deficits recovered to baseline after DMPA-IM was discontinued. Recovery to baseline required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. However, it is important to note that a large number of subjects discontinued from the study, therefore these results are based on a small number of subjects and some subjects still had deficit in total hip BMD after 240 weeks. Longer duration of treatment and smoking were associated with slower recovery. Please refer to Table 3 below.

Table 3. Mean Percentage Changes from Baseline (with 95% Confidence Intervals) in BMD in Adolescents after Discontinuation of DMPA

Week after DMPA discontinuation	N	Median Number of Injections	Mean % Change (SE) From Baseline to End of Treatment	95% CI	Mean % change (SE) from baseline to post-DMPA visit	95% CI
Total hip BMD						
0	98	9	-4.1 (0.43)	[-4.95; -3.25]	N/A	
24	74	9	-4.1 (0.53)	[-5.15; -3.04]	-4.0 (0.61)	[-5.25; -2.80]
60	71	8	-3.6 (0.46)	[-4.48; -2.66]	-2.8 (0.56)	[-3.97; -1.72]
120	52	10	-4.3 (0.64)	[-5.56; -2.98]	-1.7 (0.72)	[-3.14; -0.26]
180	39	7	-4.1 (0.72)	[-5.55; -2.63]	-1.2 (0.85)	[-2.96; 0.46]
240	25	9	-3.4 (0.67)	[-4.73; -1.98]	0.1 (0.98)	[-1.95; 2.11]
Femoral neck BMD						
0	98	9	-3.9 (0.50)	[-4.92; -2.92]	N/A	
26	74	9	-3.8 (0.60)	[-5.01; -2.62]	-4.0 (0.71)	[-5.40; -2.55]
60	71	8	-3.3 (0.56)	[-4.41; -2.18]	-3.6 (0.70)	[-4.99; -2.18]
120	52	10	-3.8 (0.74)	[-5.25; -2.28]	-1.8 (0.82)	[-3.43; -0.13]
180	39	7	-3.9 (0.85)	[-5.62; -2.17]	-1.0 (0.98)	[-3.00; 0.97]
240	25	9	-3.4 (0.80)	[-5.07; -1.78]	-0.7 (1.19)	[-3.20; 1.72]
Lumbar spine BMD						
0	98	9	-2.7 (0.39)	[-3.45; -1.91]	-N/A	
26	74	9	-2.6 (0.43)	[-3.42; -1.69]	-2.5 (0.51)	[-3.52; -1.48]
60	70	8	-2.8 (0.43)	[-3.66; -1.96]	-0.2 (0.60)	[-1.41; 1.01]
120	52	10	-2.7 (0.61)	[-3.96; -1.50]	2.2 (0.73)	[0.74; 3.67]
180	39	7	-3.0 (0.67)	[-4.35; -1.66]	2.8 (0.79)	[1.16; 4.35]
240	25	9	-2.6 (0.80)	[-4.28; -0.99]	4.5 (1.03)	[2.35; 6.61]

SE = Standard Error
CI = Confidence interval

Relationship of fracture incidence to use of DMPA-IM by women of reproductive age.

A large retrospective cohort study using data from the General Practice Research Database (GPRD) included N=41,876 women who used DMPA for contraception and had data available for 6-24 months before their first use of DMPA and for mean 5.5 years after their first DMPA injection. Fracture risk was observed to be higher overall in the DMPA cohort when compared to non-users both 'before' and 'after' DMPA use. Fracture risk was compared between the period 'after' first DMPA injection vs. the period 'before' first injection: Incident Risk Ratio=1.01 (95% CI: 0.92, 1.11), suggesting that DMPA did not increase risk for bone fracture.

Maximum follow-up in this study was 15 years; therefore, possible effects of DMPA that might extend beyond 15 years of follow-up cannot be determined. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life i.e. after menopause.

5.2 Pharmacokinetic properties

Absorption

After the intramuscular injection, medroxyprogesterone acetate is released slowly, resulting in low, but persistent levels in circulation. Immediately after the intramuscular injection of medroxyprogesterone acetate 150 mg/ml, the plasma levels were 1.7 +/– 0.3 nmol/l. Two weeks later, the levels were 6.8 +/– 0.8 nmol/l. The average time to reach the peak is approximately 4 to 20 days after the intramuscular dose. Serum levels of medroxyprogesterone acetate diminish gradually and remain relatively constant at around 1 ng/ml during 2–3 months. Levels in circulation can be detected for 7 to 9 months after the intramuscular injection.

Distribution

Medroxyprogesterone acetate is approximately 90 to 95% plasma protein bound. Volume of distribution is 20 +/– 3 litres. Medroxyprogesterone acetate crosses the blood-brain barrier and the placenta (see Section 4.6). Low levels of medroxyprogesterone acetate have been detected in breast milk of lactating women administered 150 mg of medroxyprogesterone acetate by the IM route (see Section 4.6).

Biotransformation

Medroxyprogesterone acetate is metabolised in the liver.

Elimination

The elimination half-life following an intramuscular injection is about 6 weeks. Medroxyprogesterone acetate is primarily excreted in the faeces, via biliary secretion. Approximately 30% of an intramuscular dose is secreted in the urine after 4 days.

5.3 Preclinical safety data

Carcinogenicity, mutagenicity, reduction of fertility

Repeated intramuscular administration of medroxyprogesterone acetate caused an increase in breast tumours in dogs.

Medroxyprogesterone acetate was not shown to be carcinogenic in rats and mice when administered orally, nor to be mutagenic in a group of tests of genetic toxicity *in vitro* and *in vivo*. Since medroxyprogesterone acetate when administered in high doses is a contraceptive drug, it is expected that high doses will reduce fertility until suspension of the treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene Glycol 3350
Sodium Chloride
Polysorbate 80
Methyl Paraben
Propyl Paraben
Sodium Hydroxide
Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Depo-Provera® 500, 150 mg/ml, suspension for injection is presented in a type 1 glass vial with a butyl rubber stopper, containing 3.3 ml (500 mg)

6.6 Special precautions for disposal and other handling

There are no special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzeliya Pituach 46725

8. LICENSE NUMBER

013-40-24544

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