

SAYANA[®]

1. NAME OF THE MEDICINAL PRODUCT

SAYANA[®]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA[®] single-dose pre-filled syringe containing 104 mg depot medroxyprogesterone acetate (DMPA) in 0.65 ml suspension for injection.

Excipients with known effect:

Methyl parahydroxybenzoate – 1.04 mg per 0.65 ml

Propyl parahydroxybenzoate – 0.0975 mg per 0.65 ml

Sodium – 2.47 mg per 0.65 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for subcutaneous injection

White to off-white homogeneous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SAYANA[®] is indicated for long-term female contraception. Each subcutaneous injection prevents ovulation and provides contraception for at least 13 weeks (+/-1 week). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4).

Since loss of bone mineral density (BMD) may occur in females of all ages who use SAYANA[®] long-term (see section 4.4), 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 Adolescents (12-18 years)

In adolescents, use of SAYANA[®] is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with SAYANA[®] during the critical period of bone accretion (see section 4.4).

SAYANA[®] has not been studied in women under the age of 18 years but data are available for intramuscular MPA in this population.

4.2 Posology and method of administration

The pre-filled syringe of SAYANA[®] should be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension. The treatment should be initiated by a doctor or healthcare assistant and administered as a subcutaneous injection (SC) into the anterior thigh or

abdomen. The medication should be injected slowly until the syringe is empty, which should take about 5-7 seconds. For instructions on how to prepare SAYANA[®] before administration, and how to administer SAYANA[®], see section 5.4.

Adults

First Injection: To provide contraceptive cover in the first cycle of use, an injection of 104 mg SC should be given during the first five days of a normal menstrual cycle. If the injection is carried out according to these instructions, no additional contraceptive measure is required.

Further Doses: The second and subsequent injections should be given at 13-week intervals, as long as the injection is given no later than seven days after this time, no additional contraceptive measures (e.g., barrier) are required. If the interval from the preceding injection is greater than 14 weeks (13 weeks plus 7 days) for any reason, then pregnancy should be excluded before the next injection is given. The efficacy of SAYANA[®] depends on adherence to the recommended dosage schedule of administration.

Post Partum: If the patient is not breast-feeding, the injection should be given within 5 days post partum (to increase assurance that the patient is not pregnant). If the injection is to be given at another time, then pregnancy should be excluded.

If the patient is breast-feeding, the injection should be given no sooner than six weeks post partum, when the infant's enzyme system is more developed (see section 4.6).

There is evidence that women prescribed SAYANA[®] in the immediate puerperium can experience prolonged and heavy bleeding. Because of this, the drug should be used with caution in the puerperium. Women who are considering use of the product immediately following delivery or termination should be advised that the risk of heavy or prolonged bleeding may be increased. Doctors are reminded that in the non-breast-feeding, post partum patient, ovulation may occur as early as week 4.

Switching from other Methods of Contraception: When switching from other contraception methods, SAYANA[®] should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods (e.g., patients switching from oral contraceptives should have their first injection of SAYANA[®] within 7 days after their last active pill).

Hepatic impairment: The effect of hepatic disease on the pharmacokinetics of SAYANA[®] is unknown. As SAYANA[®] largely undergoes hepatic elimination, it may be poorly metabolised in patients with severe liver insufficiency (see section 4.3 Contraindications).

Renal impairment: The effect of renal disease on the pharmacokinetics of SAYANA[®] is unknown. No dosage adjustment should be necessary in women with renal insufficiency, since SAYANA[®] is almost exclusively eliminated by hepatic metabolism.

Paediatric Population

SAYANA[®] is not indicated before menarche (see section 4.1 Therapeutic Indications). Data in adolescent females (12-18 years) is available for IM administration of MPA (see section 4.4 Special Warnings and Precautions for Use and section 5.1 Pharmacodynamic properties). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA[®] is expected to be the same for adolescents after menarche and adult females.

4.3 Contraindications

- SAYANA[®] is contra-indicated in patients with a known hypersensitivity to MPA or any of its excipients listed in section 6.1.
- SAYANA[®] is contra-indicated if pregnancy is known or suspected.

- SAYANA[®] is contra-indicated in women with known or suspected malignancy of the breast or genital organs.
- SAYANA[®] is contra-indicated in patients with undiagnosed vaginal bleeding.
- SAYANA[®] is contra-indicated in patients with severe hepatic impairment.
- SAYANA[®] is contra-indicated in patients with metabolic bone disease.
- SAYANA[®] is contra-indicated in patients with active thromboembolic disease and in patients with current or past history of cerebrovascular disease.

4.4 Special warnings and precautions for use

Loss of Bone Mineral Density

Use of depot medroxyprogesterone acetate subcutaneous (DMPA-SC) reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use; however, BMD appears to increase after DMPA-SC is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of DMPA-SC by younger women will reduce peak bone mass and increase the risk for fracture in later life i.e., after menopause.

A study to assess the BMD effects of DMPA-IM (Depo-Provera), in adolescent females showed that its use was associated with a statistically significant decline in BMD from baseline. After discontinuing DMPA-IM in adolescents, return of mean BMD to baseline values 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.

In adolescents, SAYANA[®] may be used but only after other methods of contraception have been discussed with the patients and considered to be unsuitable or unacceptable.

A large observational study of predominantly adult female contraceptive users showed that use of DMPA-IM did not increase risk for bone fractures. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life (see section 5.1 – Relationship of fracture incidence to use of DMPA-IM by women of reproductive age).

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years. In particular, in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of SAYANA[®].

Significant risk factors for osteoporosis include:

- Alcohol abuse and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Previous low trauma fracture
- Family history of osteoporosis

For further information on BMD changes in both adult and adolescent females, refer to section 5.1. Adequate intake of calcium and vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Menstrual Irregularities

Most women using SAYANA[®] experienced alteration of menstrual bleeding patterns. Patients should be appropriately counseled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. As women continued using SAYANA[®], fewer experienced irregular bleeding and more experienced amenorrhea. After receiving the fourth dose, 39% of women experienced

amenorrhea during month 6. During month twelve, 56.5% of women experienced amenorrhea. The changes in menstrual patterns from the three contraception trials are presented in Figures 1 and 2. Figure 1 shows the increase in the percentage of women experiencing amenorrhea over the 12-month study. Figure 2 presents the percentage of women experiencing spotting only, bleeding only, and bleeding and spotting over the same time period. In addition to amenorrhea, altered bleeding patterns included intermenstrual bleeding, menorrhagia and metrorrhagia. If abnormal bleeding associated with SAYANA® persists or is severe, appropriate investigation and treatment should be instituted.

Figure 1. Percent of SAYANA®-Treated Women with Amenorrhea per 30-Day Month Contraception Studies (ITT Population, N=2053)

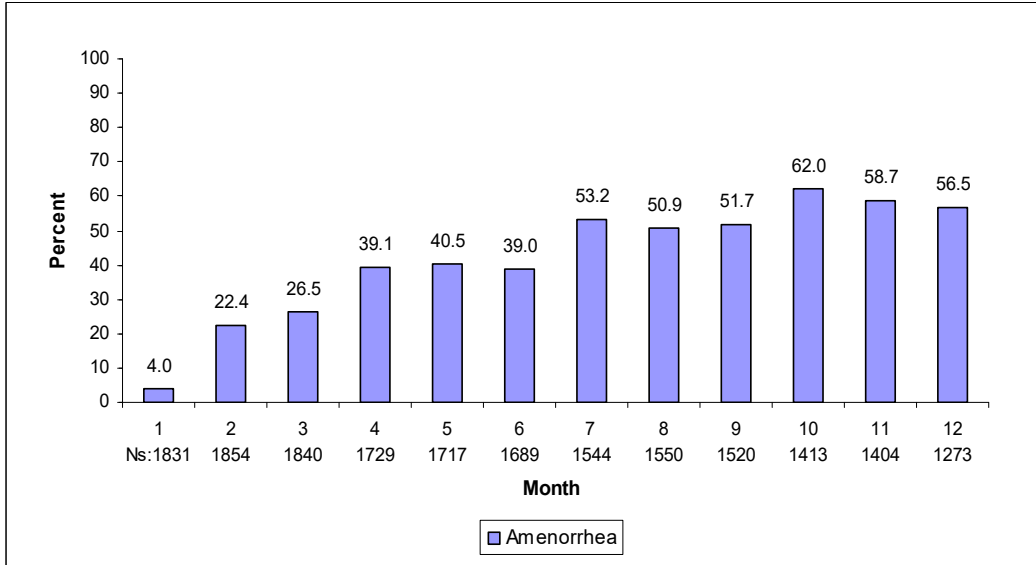
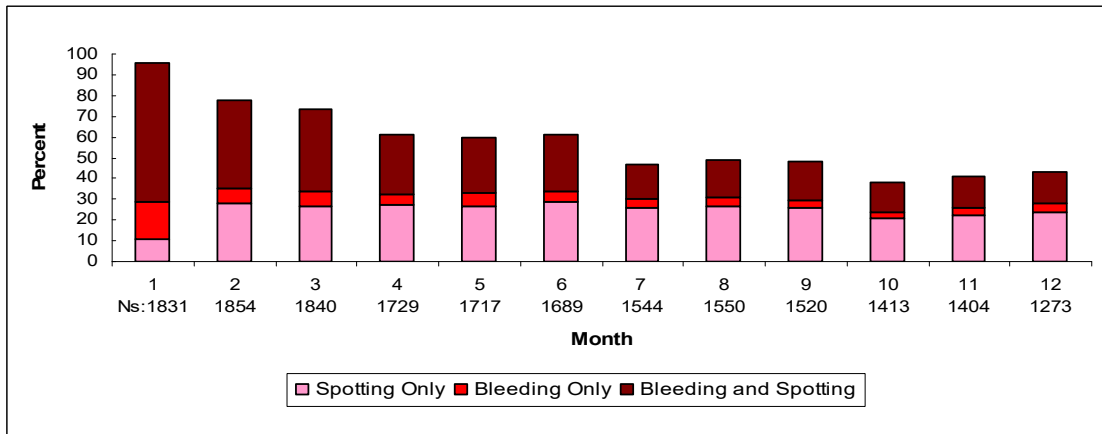


Figure 2. Percent of SAYANA® -Treated Women with Bleeding and/or Spotting per 30-Day Month Contraception Studies (ITT Population, N=2053)



Cancer Risks

Long-term case-controlled surveillance of DMPA-IM 150 mg users found no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users.

Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives.

Results from some epidemiological studies suggest a small difference in the risk of having the disease in current and recent users compared with never-users. Any excess risk in current and recent DMPA

users is small in relation to the overall risk of breast cancer, particularly in young women (see below), and is not apparent after 10 years since last use. Duration of use does not seem to be important.

Possible number of additional cases of breast cancer diagnosed up to 10 years after stopping injectable progestogens*

Age at last use of DMPA	No. of cases per 10,000 women who are never-users	Possible additional cases per 10,000 DMPA users
20	Less than 1	Much less than 1
30	44	2-3
40	160	10

* based on use for 5 years

Thromboembolic Disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops such an event, e.g., pulmonary embolism, cerebrovascular disease, retinal thrombosis or deep venous thrombosis, while undergoing therapy with SAYANA® should not be re-administered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SAYANA® use in this population.

Anaphylaxis and Anaphylactoid Reaction

If an anaphylactic reaction occurs, appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

Ocular Disorders

Medication should not be re-administered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be re-administered.

Precautions

Weight Changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Fluid Retention

There is evidence that progestogens may cause some degree of fluid retention, and as a result, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.

Return of Ovulation

Following a single dose of SAYANA®, the cumulative rate of return to ovulation as measured by plasma progesterone was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, and the median time to ovulation was 30 weeks. Women should be counseled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity, especially polycystic ovarian syndrome.

Psychiatric Disorders

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and

suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Protection against Sexually Transmitted Infections

Women should be counselled that SAYANA[®] does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to STIs. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

The benefits of contraceptive options and their risks must be evaluated individually for each woman.

Carbohydrate/Metabolism

Some patients receiving progestogens may exhibit a decrease in glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.

Liver Function

If jaundice develops in any woman receiving SAYANA[®], consideration should be given to not re-administer the medication (see section 4.3).

Hypertension and Lipid Disorders

Limited evidence suggests that there is a small increased risk of cardiovascular events among women with hypertension or with lipid disorders who used progestogen-only injectables. If hypertension occurs under SAYANA[®] treatment and/or the increase in hypertension cannot adequately be controlled by antihypertensive medication, treatment with SAYANA[®] should be stopped. Additional risk factors for arterial thrombotic disorders include: hypertension, smoking, age, lipid disorders, migraine, obesity, positive family history, cardiac valve disorders, atrial fibrillation.

SAYANA[®] should be used cautiously in patients with one or more of these risk factors.

Other Conditions

The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestagens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

If any of the conditions/risk factors mentioned is present, the benefits of SAYANA[®] use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether SAYANA[®] use should be discontinued.

Laboratory Tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components might be affected by progestogen therapy:

- a) Plasma/urinary steroids are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol).
- b) Plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH).
- c) Sex-hormone-binding-globulin (SHBG) concentrations are decreased.

Excipients

As this product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm. This medicinal product contains less than 1 mmol sodium (23 mg) per 104 mg/0.65 ml, i.e., essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with SAYANA®.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

MPA is metabolized *in vitro* primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with 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

Fertility

SAYANA® is indicated for the prevention of pregnancy. Women may experience a delay in return to fertility (conception) following discontinuation of SAYANA® (see section 4.4).

Pregnancy

SAYANA® is contraindicated in women who are pregnant. Some reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. If SAYANA® is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

One study found that infants from unintentional pregnancies that occurred 1 to 2 months after injection of DMPA-IM (150 mg) were at an increased risk of low birth weight; this, in turn, has been associated with an increased risk of neonatal death. However, the overall risk of this is very low because pregnancies while on DMPA-IM (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with DMPA-IM (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted. However, due to limitations of the data regarding the effects of MPA in breastfed infants less than six weeks old, SAYANA® should be given no sooner than six weeks post partum when the infant's enzyme system is more developed.

4.7 Effects on ability to drive and use machines

SAYANA® has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Events from clinical trials:

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled 2053 women who received DMPA-SC for contraception. The most frequently (>5%) reported adverse drug reactions were headache (8.9%), metrorrhagia (7.1%), weight increased (6.9%), amenorrhoea (6.3%) and injection site reactions (any type, 6.1%).

Adverse reactions are listed according to the following categories. These are as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Frequency not known (cannot be estimated from the available data)

Events from post-marketing surveillance:

In addition, adverse events of medical significance obtained from post-marketing data with the use of injectable DMPA (IM or SC) are also included in the list below:

<u>System organ class</u>	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>	<u>Not known</u>
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>				Breast cancer (see section 4.4)	
<i>Immune system disorders</i>			Drug hypersensitivity (see section 4.4)		Anaphylactic reaction, Anaphylactoid reaction, Angioedema (see section 4.4)
<i>Metabolism and nutrition disorders</i>			Fluid retention (see section 4.4), Increased appetite, Decreased appetite		
<i>Psychiatric disorders</i>		Depression, Insomnia, Anxiety, Affective disorder, Irritability, Libido decreased	Nervousness, Emotional disorder, Anorgasmia		
<i>Nervous system disorders</i>		Dizziness, Headache	Migraine, Somnolence		Seizure
<i>Ear and labyrinth disorders</i>			Vertigo		
<i>Cardiac disorders</i>			Tachycardia		
<i>Vascular disorders</i>			Hypertension (see section 4.4), Varicose vein, Hot flush		Pulmonary embolism, Embolism and thrombosis (see section 4.4), Thrombophlebitis
<i>Gastrointestinal disorders</i>		Abdominal pain, Nausea	Abdominal distension		
<i>Hepatobiliary disorders</i>					Jaundice, Hepatic function abnormal (see section 4.4)
<i>Skin and subcutaneous tissue disorders</i>		Acne	Alopecia, Hirsutism, Dermatitis,	Lipodystrophy acquired	Skin striae

			Ecchymosis, Chloasma, Rash, Pruritus, Urticaria		
<i>Musculoskeletal and connective tissue disorders</i>		Back pain, Pain in extremity	Arthralgia, Muscle spasms		Osteoporosis, Osteoporotic fractures
<i>Reproductive system & breast disorders</i>		Menometrorrhagia, Metrorrhagia , Menorrhagia (see section 4.4), Dysmenorrhoea, Amenorrhoea, Vaginitis, Breast pain	Ovarian cyst, Uterine haemorrhage (irregular, increase, decrease), Vaginal discharge, Dyspareunia, Galactorrhoea, Pelvic pain, Vulvovaginal dryness, Premenstrual syndrome, Breast tenderness, Breast enlargement		
<i>General disorders and administration site conditions</i>		Fatigue, Injection site reaction, Injection site persistent atrophy/inde ntation/ dimpling, Injection site nodule/lump, Injection site pain/ tenderness	Pyrexia	Asthenia, Injection site discolouration	
<i>Investigations</i>		Weight increased (see section 4.4), Smear cervix abnormal	Bone density decreased (see section 4.4), Glucose tolerance decreased (see section 4.4), Hepatic enzyme abnormal	Weight decreased (see section 4.4)	

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

No positive action is required other than cessation of therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: G03AC06

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

DMPA-SC inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus. These actions produce its contraceptive effect.

BMD Changes in Adult Women

A study comparing changes in BMD in women using DMPA-SC with women using DMPA-IM showed similar BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the DMPA-SC group are listed in Table 1.

Table 1. Mean Percent Change (with 95% Confidence Intervals) from Baseline in BMD in Adult Women Using DMPA-SC by Skeletal Site

Time on Treatment	Lumbar Spine		Total Hip		Femoral Neck	
	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)	N	Mean % Change (95% CI)
1 year	166	-2.7 (-3.1 to -2.3)	166	-1.7 (-2.1 to -1.3)	166	-1.9 (-2.5 to -1.4)
2 years	106	-4.1 (-4.6 to -3.5)	106	-3.5 (-4.2 to -2.7)	106	-3.5 (-4.3 to -2.6)

CI = Confidence Interval

In another 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 use, 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 2 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 DMPA injections, mean BMD had increased at all 3 skeletal sites but deficits remained (see Table 2 below).

Table 2. 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) 95% CI	(3.57) -6.65; -4.11	(3.27) -0.20; 1.06	(3.60) -6.80; -3.52	(3.18) -0.60; 0.98	(4.68) -7.75; -4.49	(5.22) -1.27; 0.73
7 years** n	12	60	7	39	13	63
Mean	-3.1%	0.5%	-1.3%	0.9%	-5.4%	-0.0%
(SD) 95% CI	(3.15) -5.13; -1.13	(3.65) -0.39; 1.49	(4.95) -5.92; 3.23	(3.81) -0.29; 2.17	(2.73) -7.03; -3.73	(5.88) -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 a hormonal contraceptive for 7 years.

SD = Standard Deviation

CI = Confidence Interval

BMD Changes in Adolescent Females (12-18 years)

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 medroxyprogesterone acetate 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 3. 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 3: 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; -4.65]
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 4. 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 mean BMD deficits recovered to baseline after DMPA-IM was discontinued. Recovery to baseline required 1 year 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 4 below.

Table 4: Mean Percentage Changes (with 95% Confidence Intervals) from Baseline 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	
24	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	
24	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 (150 mg) 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., following the menopause.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of MPA following a single SC injection of SAYANA[®] are shown in Table 5.

Table 5. Pharmacokinetic Parameters of MPA After a Single SC Injection of SAYANA[®] in Healthy Women (n=42)

	C _{max} (ng/ml)	T _{max} (day)	C _{91 (min)} (ng/ml)	AUC ₀₋₉₁ (ng·day/ml)	AUC _{0-∞} (ng·day/ml)	t _{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

General Characteristics

Absorption

MPA absorption from the SC injection site to achieve therapeutic levels is relatively prompt. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/ml, with a mean C_{max} of 1.5 ng/ml after a single SC injection.

Effect of Injection Site

SAYANA[®] was administered into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin; no binding of MPA occurs with SHBG.

Biotransformation

MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Elimination

Residual MPA concentrations at the end of the dosing interval (3 months) of SAYANA[®] are generally below 0.5 ng/ml, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates, with only small amounts excreted as sulfates.

Linearity/Non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special Populations

Race

There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA[®] among women of all ethnic backgrounds studied. The pharmacokinetics/dynamics of MPA has been evaluated in Asian women in a separate study.

Effect of Body Weight

No dosage adjustment of SAYANA[®] is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng-day/ml in women with BMI categories of ≤25 kg/m², >25 to ≤30 kg/m², and >30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/ml in women with BMI ≤25 kg/m², 1.76 ng/ml in women with BMI >25 to ≤30 kg/m², and 1.40 ng/ml in women with BMI >30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Pharmacokinetic/Pharmacodynamic Relationship(s)

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13-week dosing interval.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Medroxyprogesterone acetate has been shown to have adverse effects on reproduction in animals and is contraindicated for use during pregnancy.

5.4 Instructions for administration

The following information is intended for medical or healthcare professionals only:

Introduction

SAYANA[®] should be administered by a healthcare professional, such as your doctor, nurse or healthcare assistant who is trained in administering subcutaneous injections.

SAYANA[®] should be administered as a subcutaneous injection (SC) into the anterior thigh or abdomen.

The following instructions explain how to prepare and inject SAYANA[®].

The instructions should be read carefully and followed step-by-step.

The injection should not be mixed with any other medicine.

Instructions for Administration of SAYANA[®] for Subcutaneous Use –

Getting ready:

Do not refrigerate. Ensure that the medication **is at room temperature** prior to injection (to ensure appropriate viscosity of the suspension). Make sure the following components (Diagram 1) are available.

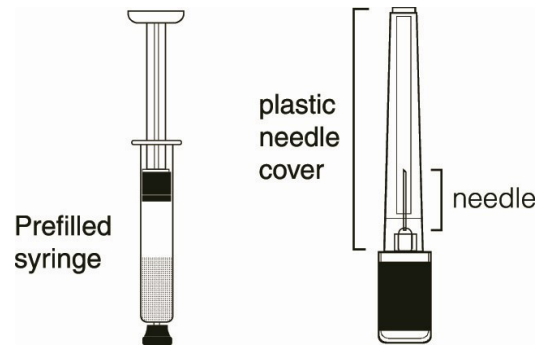


Diagram 1

SAYANA[®], as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

Syringe preparation:

Gently twist off the protective end cap from the needle to break the seal (Diagram 2). Set aside.



Diagram 2

While holding the syringe firmly by the barrel pointing upward, shake it vigorously for at least 1 minute to thoroughly mix the medication (Diagram 3).

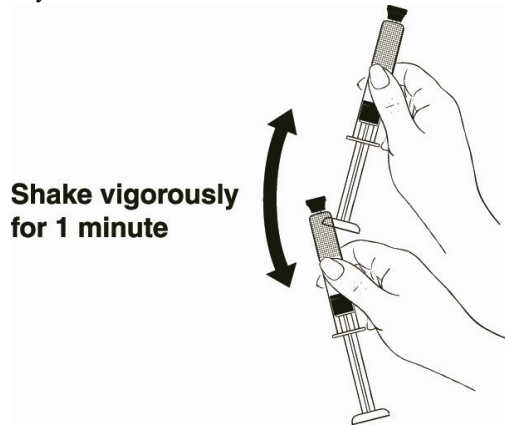


Diagram 3

Shake vigorously for 1 minute

Then remove the protective cap from the tip of the syringe barrel. While holding the syringe barrel, attach the needle to the barrel of the syringe firmly by pushing the plastic needle cover down fully with a slight twisting movement (Diagram 4).

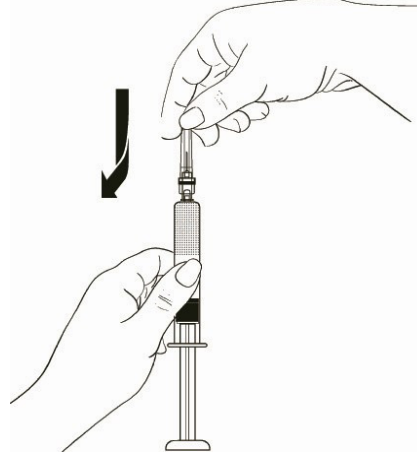


Diagram 4

Administration:

Step 1: Choosing and preparing the injection area.

Choose the injection area in either the upper thigh or abdomen, see shaded areas (Diagram 5). Avoid bony areas and the umbilicus.

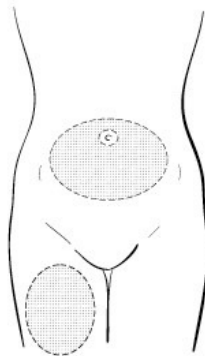


Diagram 5

Upper thigh or abdomen.

Use an alcohol pad to wipe the skin in the injection area you have chosen. Allow the skin to dry.

While continuing to hold the syringe barrel firmly, remove the clear protective plastic cover from the needle without twisting, making sure the needle is still firmly attached to the syringe (Diagram 6).

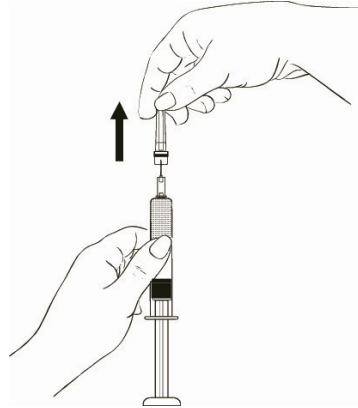


Diagram 6

While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe. There should be no air within the barrel (Diagram 7).

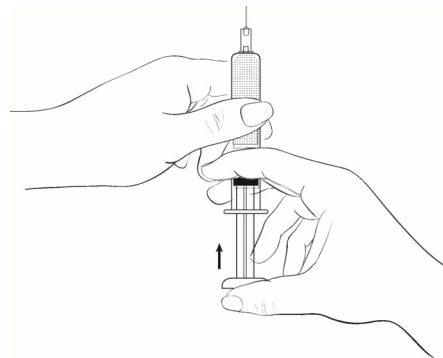


Diagram 7

Step 2: Injecting the dose.

Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and fore-finger (Diagram 8), pulling it away from the body.



Diagram 8

Insert the needle at a 45-degree angle so that most of the needle is in the fatty tissue. The plastic hub of the needle should be nearly or almost touching the skin (Diagram 9).

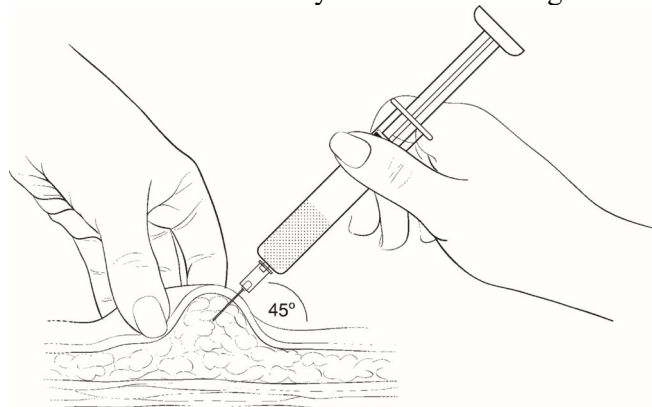


Diagram 9

Inject the medication slowly until the syringe is empty (Diagram 10). This should take about 5-7 seconds. It is important that the entire dose of SAYANA® is given.

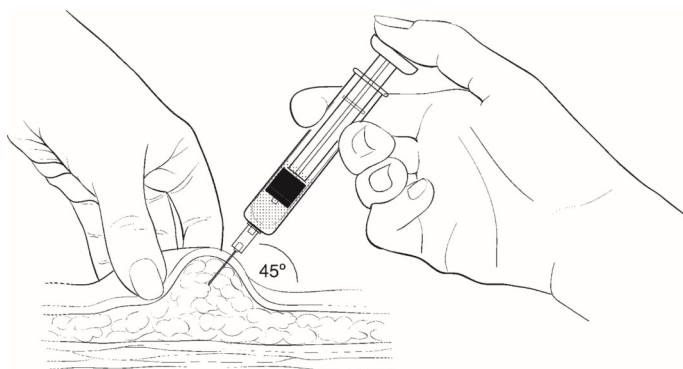


Diagram 10

Inject slowly (5-7 seconds)

When the entire dose is completely injected, gently pull the needle out of the skin. Use a clean cotton pad to press lightly on the injection area for a few seconds.

Do NOT rub the area.

Following the administration of each dose, the used syringe should be discarded in a safe and proper manner.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350
Sodium Chloride
Povidone

Sayana LPD Israel CC 161023
Polysorbate 80
Methyl Parahydroxybenzoate (E 218)
Methionine
Monobasic Sodium Phosphate
Disodium Phosphate Dodecahydrate
Propyl Parahydroxybenzoate (E 216)
Hydrochloric Acid and/or Sodium Hydroxide for pH Adjustment
Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.
Once opened: use immediately. Discard any unused portion.

6.4 Special precautions for storage

Store below 25°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA[®] suspension for injection is supplied as a disposable pre-filled syringe (type 1 glass Ph.Eur.) with plunger stopper and tip cap (bromobutyl rubber). A 26G, 3/8" needle is included separately.

6.6 Instructions for use/handling and disposal

For single use only.

Any unused product should be disposed of safely after use, in accordance with local guidance for the disposal of sharps.

7. LICENSE HOLDER

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

8. LICENSE NUMBER

143-81-32952

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