SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SAYANA PRESS 104 mg/0.65 ml suspension for injection.

SUMMARY OF PRODUCT CHARACTERISTICS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS single-dose container with 104 mg medroxyprogesterone acetate (MPA) 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

Polysorbate 80 - 1.95 mg per 0.65 ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suspension for injection

White to off-white homogeneous suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

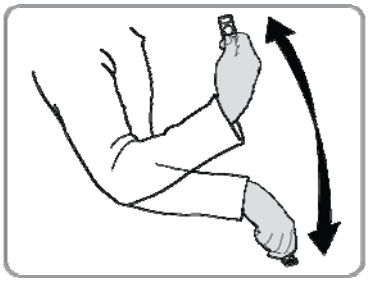
SAYANA PRESS has not been studied in women under the age of 18 years but data are available for intramuscular depot-medroxyprogesterone acetate (DMPA-IM) 150mg in this population.

4.2 Posology and method of administration

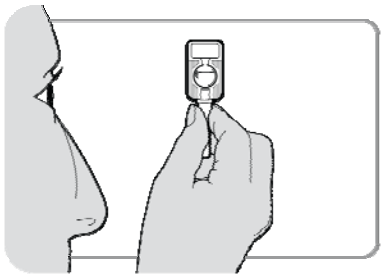
SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional (HCP). After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate and with medical follow-up as necessary.

The SAYANA PRESS single-dose container should be at room temperature. It must be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension. The contents are completely sealed inside the reservoir of the injector. The injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid. The dose is administered as a subcutaneous injection (SC) into the anterior thigh or abdomen. When the injection is being given, the injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. The medication should be injected slowly for 5-7 seconds.

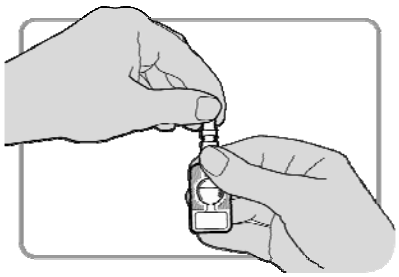
Mixing the medicine • Ensure that the SAYANA PRESS single-dose container is at room temperature. • Hold the injector firmly by the port. • Shake the injector vigorously for at least 30 seconds to mix the medicine.	

- The medicine should appear white and uniform. If it is not, discard the injector and use a new one.
- If you see liquid leaking out or any other problem, discard the injector and use a new one.
- If there is a delay before injecting, you must repeat the mixing step.

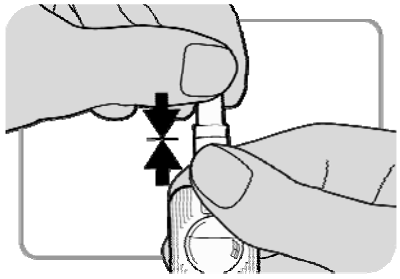


Activating the injector

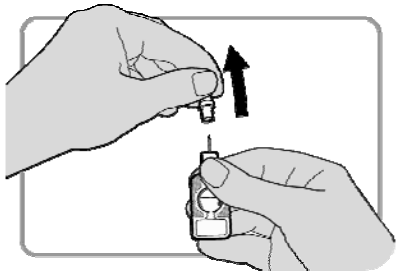
- Hold the injector firmly by the port, making sure the needle shield is pointing upwards. Take care not to squeeze the reservoir.
- Hold the needle shield with the other hand.



- Push the needle shield firmly towards the port until it will go no further. The injector is now activated.



- Pull the needle shield off, and discard it.



Please refer to the Instructions for Use included with the Patient Leaflet for full details on preparing and giving an injection

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 PRESS depends on adherence to the recommended dosage schedule of administration.

Women should be re-evaluated periodically as clinically appropriate at least every year to determine if SAYANA PRESS is still the best option for them.

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 the 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 PRESS 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 PRESS 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 PRESS within 7 days after their last active pill).

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

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

Paediatric population

SAYANA PRESS is not indicated before menarche (see section 4.1). Data in adolescent females (12-18 years) is available for IM administration of MPA (see sections 4.4 and 5.1). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

4.3 Contraindications

- SAYANA PRESS is contra-indicated in patients with a known hypersensitivity to MPA or any of its excipients listed in section 6.1.
- SAYANA PRESS is contra-indicated if pregnancy is known or suspected.
- SAYANA PRESS is contra-indicated in women with known or suspected malignancy of the breast or genital organs.
- SAYANA PRESS is contra-indicated in patients with undiagnosed vaginal bleeding.
- SAYANA PRESS is contra-indicated in patients with severe hepatic impairment.
- SAYANA PRESS is contra-indicated in patients with metabolic bone disease.
- SAYANA PRESS is contra-indicated in patients with active thromboembolic disease and in patients with current or past history of cerebrovascular disease.
- SAYANA PRESS is contra-indicated in patients with meningioma or history of meningioma.

4.4 Special warnings and precautions for use

Warnings:

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 PRESS 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 PRESS.

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 DMPA subcutaneous injection experienced alteration of menstrual bleeding patterns. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. As women continued using DMPA subcutaneous injection, 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 DMPA subcutaneous injection persists or is severe, appropriate investigation and treatment should be instituted.

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

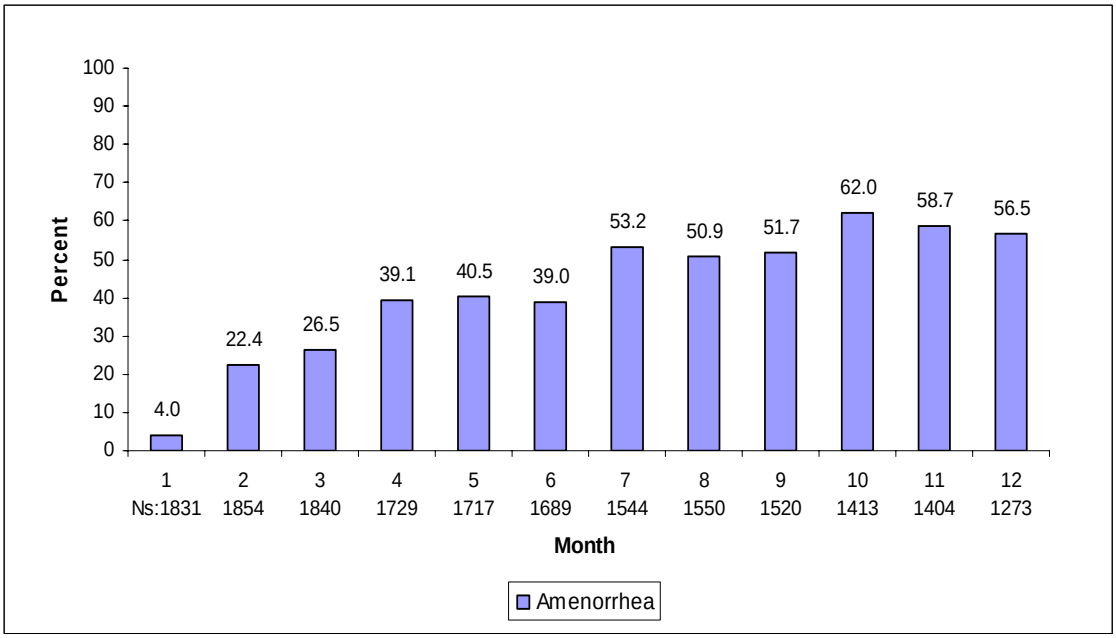
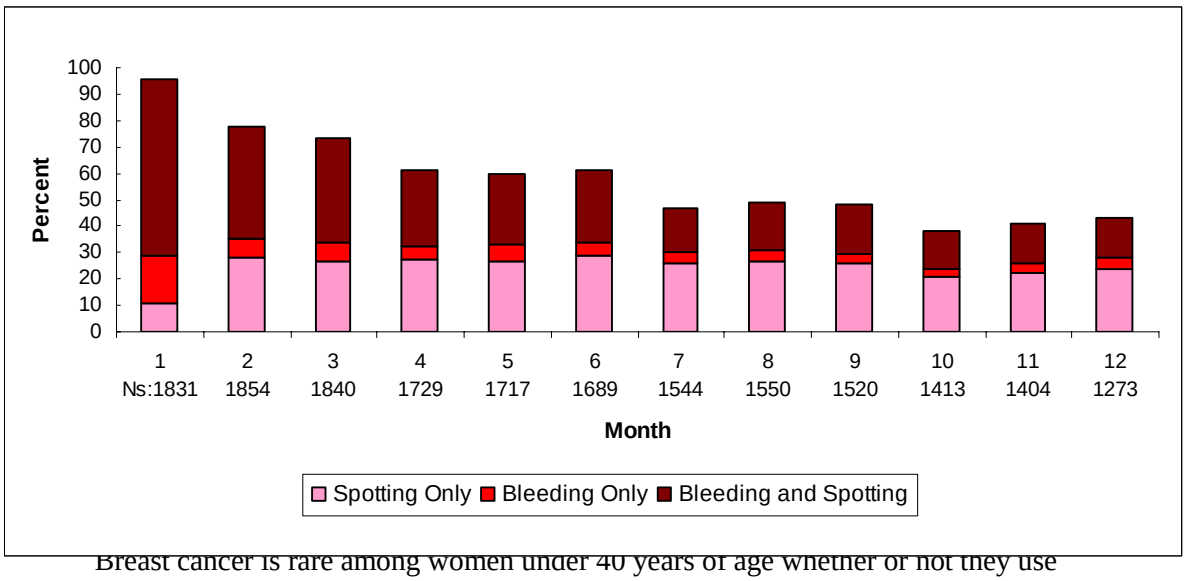


Figure 2. Percent of DMPA subcutaneous injection -Treated Women with Bleeding and/or Spotting per 30-Day Month Contraception Studies (ITT Population, N=2053)



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"

Meningioma

Cases of meningioma (single and multiple) have been reported in patients treated with medroxyprogesterone acetate for a prolonged time (several years). If a patient is diagnosed with meningioma, medroxyprogesterone acetate must be stopped, as a precautionary measure.

In some cases, shrinkage of meningioma was observed after treatment discontinuation of depot medroxyprogesterone acetate.

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 or retinal thrombosis or deep venous thrombosis, while undergoing therapy with SAYANA PRESS should not be readministered 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 PRESS 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 DMPA subcutaneous injection, 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 counselled 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 PRESS 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 PRESS, 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 PRESS treatment and/or the increase in hypertension cannot adequately be controlled by antihypertensive medication, treatment with SAYANA PRESS 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 PRESS 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 PRESS 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 PRESS 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'.
SAYANA PRESS contains polysorbate 80 (see section 2). Polysorbate 80 may cause hypersensitivity reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with SAYANA PRESS.

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 PRESS is indicated for the prevention of pregnancy.

Women may experience a delay in return to fertility (conception) following discontinuation of SAYANA PRESS (see section 4.4).

Pregnancy

SAYANA PRESS 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 PRESS 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 (150mg), 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 PRESS 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 PRESS 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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥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:

System organ class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Not known***
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Breast cancer (see section 4.4)	Meningioma
Immune system disorders			Drug hypersensitivity (see section 4.4)		Anaphylactic reaction, Anaphylactoid reaction, Angioedema (see section 4.4
Metabolism and nutrition disorders			Fluid retention (see section 4.4), Increased appetite, Decreased appetite		
Psychiatric disorders		Depression, Insomnia, Anxiety, Affective disorder, Irritability, Libido decreased	Nervousness, Emotional disorder, Anorgasmia		
Nervous system disorders		Dizziness, Headache	Migraine, Somnolence		Seizure
Ear and labyrinth disorders			Vertigo		
Cardiac disorders			Tachycardia		
Vascular disorders			Hypertension (see section 4.4),		Pulmonary embolism, Embolism and

			Varicose vein, Hot flush		thrombosis, (se section 4.4), Thrombophlebi s
Gastrointestinal disorders		Abdominal pain, Nausea	Abdominal distension		
Hepatobiliary disorders					Jaundice, Hepatic functio abnormal (see section 4.4)
Skin and subcutaneous tissue disorders		Acne	Alopecia, Hirsutism, Dermatitis, Ecchymosis , Chloasma, Rash, Pruritus, Urticaria	Lipodystrop hy acquired	Skin striae
Musculoskeletal and connective tissue disorders		Back pain, Pain in extremity	Arthralgia, Muscle spasms		Osteoporosis, Osteoporotic fractures
Reproductive system & breast disorders		Menometrorrhagi a, Metrorrhagia, Menorrhagia (see section 4.4), Dysmenorrhoea, Amenorrhoea, Vaginitis, Breast pain	Ovarian cyst, Uterine haemorrhag e (irregular, increase, decrease), Vaginal discharge, Dyspareuni a, Galactorrho ea, Vulvovagin al dryness, Premenstrua l syndrome, Breast tenderness, Breast enlargement		

General disorders and administration site conditions		Fatigue, Injection site reaction, Injection site persistent atrophy/Indentation/dimpling, Injection site nodule/lump, Injection site pain/ tenderness	Pyrexia	Asthenia, Injection site discolouration	
Investigations		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 of suspected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 year	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	33	105	21	65	34	106

***** n Mean (SD) 95% CI	-5.4% (3.57) -6.65; -4.11	0.4% (3.27) -0.20; 1.06	-5.2% (3.60) -6.80; -3.52	0.2% (3.18) -0.60; 0.98	-6.1% (4.68) -7.75; -4.49	-0.3% (5.22) -1.27; 0.73
7 years ** n Mean (SD) 95% CI	12 -3.1% (3.15) -5.13; -1.13	60 0.5% (3.65) -0.39; 1.49	7 -1.3% (4.95) -5.92; 3.23	39 0.9% (3.81) -0.29; 2.17	13 -5.4% (2.73) -7.03; -3.73	63 0.0% (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 a 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; -4.64]
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 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 1.2 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 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 24 60 120 180 240	98 74 71 52 39 25	9 9 8 10 7 9	-4.1 (0.43) -4.1 (0.53) -3.6 (0.46) -4.3 (0.64) -4.1 (0.72) -3.4 (0.67)	[-4.95; -3.25] [-5.15; -3.04] [-4.48; -2.66] [-5.56; -2.98] [-5.55; -2.63] [-4.73; -1.98]	N/A -4.0 (0.61) -2.8 (0.56) -1.7 (0.72) -1.2 (0.85) 0.1 (0.98)	[-5.25; -2.80] [-3.97; -1.72] [-3.14; -0.26] [-2.96; 0.46] [-1.95; 2.11]
Femoral Neck BMD						
0 24 60 120 180 240	98 74 71 52 39 25	9 9 8 10 7 9	-3.9 (0.50) -3.8 (0.60) -3.3 (0.56) -3.8 (0.74) -3.9 (0.85) -3.4 (0.80)	[-4.92; -2.92] [-5.01; -2.62] [-4.41; -2.18] [-5.25; -2.28] [-5.62; -2.17] [-5.07; -1.78]	N/A -4.0 (0.71) -3.6 (0.70) -1.8 (0.82) -1.0 (0.98) -0.7 (1.19)	[-5.40; -2.55] [-4.99; -2.18] [-3.43; -0.13] [-3.00; 0.97] [-3.20; 1.72]
Lumbar Spine BMD						
0 24 60 120 180 240	98 74 70 52 39 25	9 9 8 10 7 9	-2.7 (0.39) -2.6 (0.43) -2.8 (0.43) -2.7 (0.61) -3.0 (0.67) -2.6 (0.80)	[-3.45; -1.91] [-3.42; -1.69] [-3.66; -1.96] [-3.96; -1.50] [-4.35; -1.66] [-4.28; -0.99]	N/A -2.5 (0.51) -0.2 (0.60) 2.2 (0.73) 2.8 (0.79) 4.5 (1.03)	[-3.52; -1.48] [-1.41; 1.01] [0.74; 3.67] [1.16; 4.35] [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.
Meningioma

Based on results from a French epidemiological case-control study, an association between
medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French National health data system (SNDS - Systéme National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3ml injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 ml (9/18 061 (0.05%) v 11/90 305 (0.01 %), OR 5.55 (95% CI 2.27 to 13.56)). This excess risk seems to be driven primarily by prolonged use (≥ 3 years) of medroxyprogesterone acetate.

Based on results from a matched case–control study from the United States, medroxyprogesterone acetate use was associated with increased odds of the presence of meningioma with evidence of increased odds with increasing duration of use. Data were obtained from the IBM MarketScan claims database for the years 2006–2022. A total of 117,503 cases and 1,072,907 matched controls were included in the analysis. For all meningiomas, the prevalence of oral exposure to medroxyprogesterone acetate was similar between cases (2.38%) and controls (2.29%). In both crude and adjusted models, medroxyprogesterone acetate exposure was not associated with being a case (adjusted OR 0.97, 95% CI 0.93–1.01); this null association persisted across all duration categories.

The prevalence of injection exposure to medroxyprogesterone acetate was nearly twice as high among cases (0.67%) than controls (0.39%); medroxyprogesterone acetate exposure was associated with 76% increased odds of being a case (OR 1.76, 95% CI 1.63–1.90), an association that persisted in the adjusted model (OR 1.53, 95% CI 1.40–1.67). There was evidence of increased odds by duration of exposure (linear trend, p <0.0001). This association was notably specific to injection exposure to medroxyprogesterone acetate and cerebral meningiomas. No association was observed for oral medroxyprogesterone acetate exposure or for spinal meningiomas (for both oral and injection medroxyprogesterone acetate exposure).

5 PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of MPA following a single SC injection of DMPA are shown in Table 5.

Table 5. Pharmacokinetic Parameters of MPA

After a Single SC Injection of DMPA in Healthy Women (n = 42)

	C_{max} (ng/ml)	T_{max} (day)	$C_{91\ (min)}$ (ng/ml)	AUC_{0-91} (ng·day/ml)	$AUC_{0-\infty}$ (ng·day/ml)	t½ (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; AUC_{0-91} = area under the concentration-time curve over 91 days; t½ = terminal half-life; 1 nanogram = 10^3 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/mLlafter a single SC injection.

Effect of Injection Site

DMPA was administered subcutaneously 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 DMPA subcutaneousinjection 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 DMPA 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 PRESS 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/m^2). The AUC_{0-91} values for MPA were 68.5, 74.8, and 61.8 ng -day/ml in women with BMI categories of ≤ 25 kg/m^2, >25 to ≤30 kg/m^2, and >30 kg/m^2, respectively. The mean MPA C_{max} was 1.65 ng/ml in women with BMI ≤ 25 kg/m^2, 1.76 ng/ml in women with BMI >25 to ≤30 kg/m^2, and 1.40 ng/ml in women with BMI > 30 kg/m^2, 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 13week 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. Medroxyprogestrone acetate has been shown to have adverse effects on reproduction in animals and is contraindicated for use during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350
Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)
Sodium Chloride
Polysorbate 80
Monobasic Sodium Phosphate Monohydrate
Disodium Phosphate Dodecahydrate
Methionine
Povidone
Hydrochloric Acid and/or Sodium Hydroxide for pH adjustment
Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 3 years

Once opened: use immediately, discard any unused portion

6.4 Special precautions for storage

Do not refrigerate or freeze

6.5 Nature and contents of container

SAYANA PRESS suspension for injection is supplied in a single-dose container in the form of a pre-filled injector containing 0.65 ml. The injector comprises a linear low density polyethylene laminate reservoir with a siliconized AISI Type 304 Stainless Steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

The pack sizes are:

- one single-dose container
- 200 single-dose containers

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Sandwich

Kent

CT13 9NJ

United Kingdom

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