PT. Pfizer Indonesia
Local Product Document

Generic Name: Medroxyprogesterone Acetate
Trade Name: SAYANA® PRESS
CDS Effective Date: November 01, 2019
Supersedes: July 17, 2017

1. NAME OF THE MEDICINAL PRODUCT

1.1. Product name
SAYANA® PRESS

1.2. Strength
104 mg/0.65 mL

1.3. Pharmaceutical dosage form
White to off-white suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration
SAYANA® PRESS 104 mg/0.65 mL injectable suspension is a single dose container. It contains 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL.

2.2. Quantitative declaration
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for subcutaneous (SC) injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SAYANA® PRESS is indicated for 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.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use SAYANA® PRESS injection long-term, a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

4.2 Posology and method of administration

Injectable suspensions should be shaken well before use.

Contraception

SAYANA® PRESS should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 104 mg. SAYANA® PRESS must be given by subcutaneous injection into the anterior thigh or abdomen, every 3 months (12–14 weeks). Dosage does not need to be adjusted for body weight. The SC suspension is not formulated for intramuscular injection.

Self-injection:

SAYANA® PRESS 104 mg/0.65 mL single dose container may be administered by a healthcare professional (HCP) or, when considered appropriate by the HCP, self-injected by the patient.

Administration of SAYANA® PRESS 104 mg/0.65 mL single dose container 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 104 mg/0.65 mL single dose container if their HCP determines that it is appropriate and with medical follow-up as necessary.

First injection

The initial SC injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days postpartum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks postpartum.

Second and subsequent injections

If more than 14 weeks have elapsed since the last SC injection, pregnancy should be ruled out before administering the next SC injection.

When switching from other contraceptive 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 taking their last active pill).

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.

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

SAYANA® PRESS is contraindicated in patients with the following conditions:

- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known hypersensitivity to MPA or any component of the drug

- Patients with metabolic bone disease
- Patients with active thromboembolic disease and in patients with current or past history of cerebrovascular disease

Additional Contraindication(s) for Specific Use
Known or suspected malignancy of the breast or genital organs.

4.4 Special warnings and precautions for use

General

- Unexpected vaginal bleeding during therapy with MPA should be investigated.
- MPA may cause some degree of fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving MPA therapy.
- Some patients receiving MPA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.
- The pathologist (laboratory) should be informed of the patient's use of MPA if endometrial or endocervical tissue is submitted for examination.
- The physician/laboratory should be informed that use of MPA may decrease the levels of the following endocrine biomarkers:
    a. Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
    b. Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
    c. Sex hormone-binding-globulin
- Medication should not be readministered, 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 papilloedema or retinal vascular lesions, medication should not be readministered.
- MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, however, MPA is not recommended in any patient with a history of venous thromboembolism (VTE). Discontinuation of MPA is recommended in patients who develop VTE while undergoing therapy with MPA.

<u>Menstrual Irregularities</u>
Most women using DMPA subcutaneous injection 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 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)

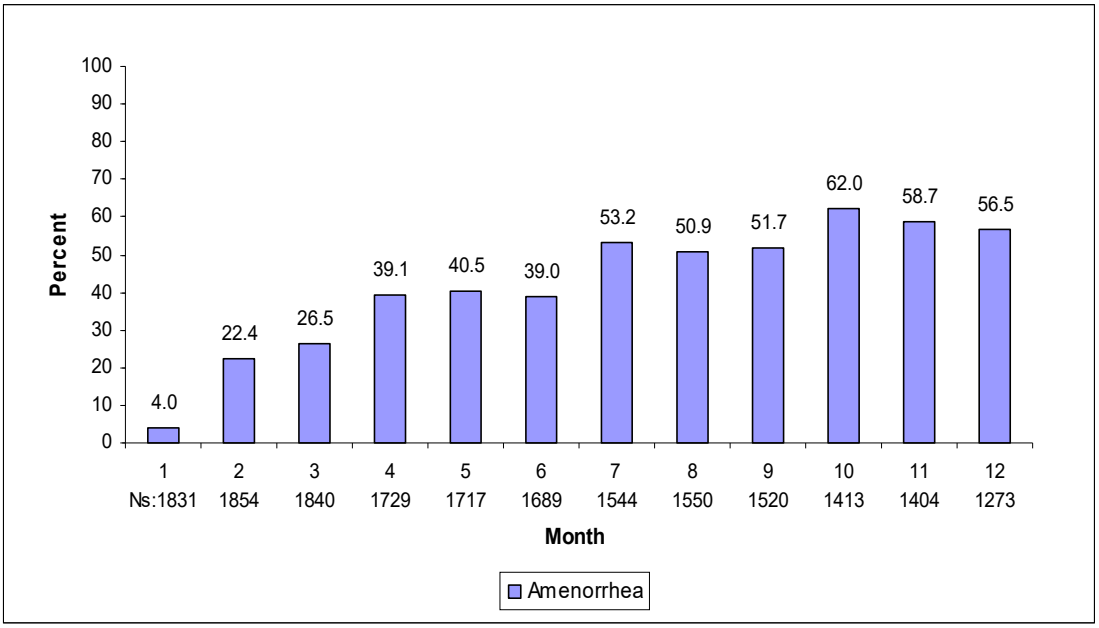
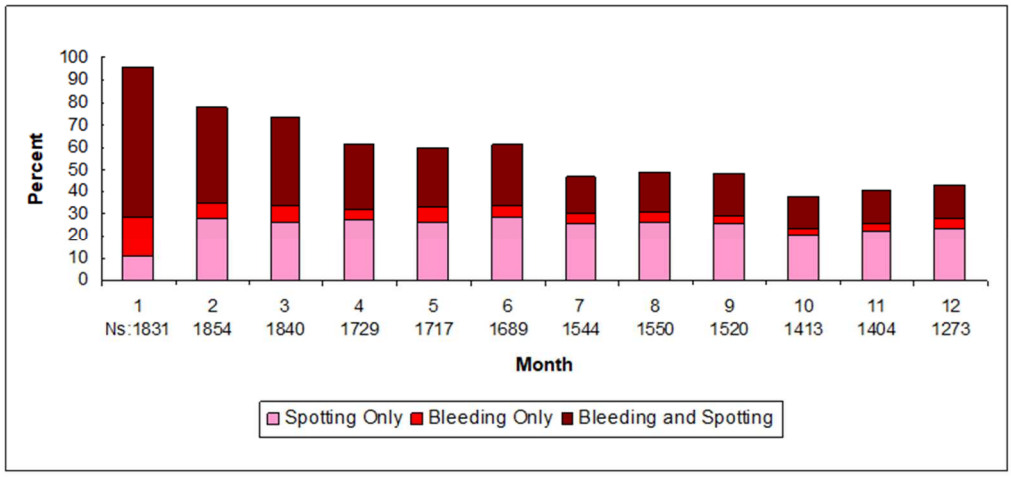


Figure 2. Percent of DMPA Subcutaneous Injection -Treated Women with Bleeding and/or Spotting per 30-Day Month Contraception Studies (ITT Population, N=2053)



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.

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 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® 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**.**

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 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 recognized, however, that amenorrhea 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.

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.

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-parahydroxbenzoate and propyl-parahydroxbenzoate, 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’.

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.

Contraception

Loss of Bone Mineral Density (BMD)

Use of DMPA (Depot-medroxyprogesterone acetate) injection reduces serum estrogen levels in premenopausal women and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of DMPA injection during adolescence and early adulthood, a critical period of bone accretion,

will reduce peak bone mass. In both adult females, the decrease in BMD during treatment appears to be substantially reversible after DMPA injection is discontinued and ovarian estrogen production increases (see section 5.1 – Pharmacodynamic properties, *Clinical Studies,* BMD Studies).

In adults, BMD was observed for a period of 2 years after DMPA injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine, female contraceptive users showed that use of Depo-Provera injection did not increase risk for bone fractures. Importantly, this study could not determine whether use of DMPA has an effect on fracture rare in life (see section 5.1 – Pharmacodynamic Properties, *Clinical Studies*, BMD Studies – Relationship of fracture incidence to use of DMPA injectable (150 mg IM) or non-use 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.

Other birth control methods should be considered in the risk/benefit analysis for the use of DMPA injection in women with osteoporotic risk factors such as:
- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- Low body mass index (BMI) or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis
- Previous low trauma fracture

It is recommended that all patients have adequate calcium and Vitamin D intake.

Contraception
- Most women using DMPA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using DMPA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea.
- Long-term case-controlled surveillance of users of DMPA injectable suspension found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer.
  There was a tendency for women to gain weight while on therapy with DMPA.
- If jaundice develops, consideration should be given to not re-administer the drug.

Sexually Transmitted Infections
Women should be counseled that DMPA injectable suspension 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 sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

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.

Pregnancy
MPA is contraindicated in women who are pregnant.

Some reports suggest under certain circumstances, an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of DMPA injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because pregnancies while on DMPA are uncommon. There is no definitive information for the other formulations of MPA, (see section 5.2 Pharmacokinetic properties - Distribution).

If the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

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 behavioral 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

The effect of medroxyprogesterone acetate on the ability to drive and use machinery has not been systematically evaluated.

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)	
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), Varicose vein, Hot flush		Pulmonary embolism, Embolism and thrombosis, (see section 4.4), Thrombophlebitis

Gastrointestinal disorders		Abdominal pain, Nausea	Abdominal distension		
Hepatobiliary disorders					Jaundice, Hepatic function abnormal (see section 4.4)
Skin and subcutaneous tissue disorders		Acne	Alopecia, Hirsutism, Dermatitis, Ecchymosis, Chloasma, Rash, Pruritus, Urticaria	Lipodystrophy acquired	Skin striae
Musculoskeletal and connective tissue disorders		Back pain, Pain in extremity	Arthralgia, Muscle spasms		Osteoporosis, Osteoporotic fractures
Reproductive system & breast disorders		Menometrorrhagia, Metrorrhagia, Menorrhagia (see section 4.4), Dysmenorrhoea, Amenorrhoea, Vaginitis, Breast pain	Ovarian cyst, Uterine haemorrhage (irregular, increase, decrease), Vaginal discharge, Dyspareunia, Galactorrhoea, Vulvovaginal dryness, Premenstrual 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	
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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medroxyprogesterone acetate (17a-hydroxy-6a-methylprogesterone acetate) is a derivative of progesterone.

Mechanism of Action

MPA is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been demonstrated to possess several pharmacologic actions on the endocrine system:

- Inhibition of pituitary gonadotropins (FSH and LH);
- Decrease of ACTH and hydrocortisone blood levels;
- Decrease of circulating testosterone;
- Decrease of circulating estrogen levels (as the result of both FSH inhibition and enzymatic induction of hepatic reductase, resulting in increased clearance of testosterone and consequent decreased conversion of androgens to estrogens).

All of these actions result in a number of pharmacological effects, as described below.

Contraception

DMPA, when administered parenterally at the recommended dose to women, 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.

Clinical Studies

BMD Studies

BMD Changes in Adult Women

In a non-randomized controlled clinical study comparing adult women using DMPA contraceptive injection (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 DMPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DMPA. Among DMPA users, BMD declined during the first 2 years of use, with little declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. There were no significant changes in BMD in the control women over the same period of time.

BMD Recovery Post-Treatment in Adult Women

In the same study population, there was partial recovery of BMD toward baseline values during the 2-year period after stopping use of DMPA injection (150 mg IM)

After 5 years of treatment with DMPA injection (150 mg IM), the mean % change in BMD from baseline was -5.4%, -5.2% and -6.1% at the spine, total hip and femoral neck, respectively, while untreated control women, over the same time interval, showed mean changes from baseline of +/- 0.5% or less at the same skeletal sites. Two years after stopping DMPA injections, mean BMD had increased at all 3 skeletal sites but deficits remained: -3.1%, -1.3% and -5.4% at the spine, total hip and femoral neck, respectively. At the same time point, women in the control group showed mean changes from baseline BMD of 0.5%, 0.9% and -0.1% at the spine, total hip and femoral neck, respectively.

5.2 Pharmacokinetic properties

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
DMPA subcutaneous 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 Sex Hormone-Binding Globulin (SHBG).

Metabolism
MPA is extensively metabolized in the liver.

Elimination
Residual MPA concentrations at the end of the dosing interval (3 months) of DMPA subcutaneous 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.

Special Populations:
Race
There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of DMPA subcutaneous among women of all ethnic backgrounds studied. The pharmacokinetics/dynamics of DMPA has been evaluated in Asian women in a separate study.

Effect of Body Weight
No dosage adjustment of DMPA subcutaneous 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 kg/m^2 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 kg/m^2 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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term intramuscular administration of medroxyprogesterone acetate (DMPA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of oral MPA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic

toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium chloride, polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection.

6.2 Incompatibilities

The injectable forms should not be mixed with any other agent.

6.3 Shelf life

Unopened : 3 years
Once opened : use immediately, discard any unused portion.

6.4 Special precautions for storage

Store at temperature below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

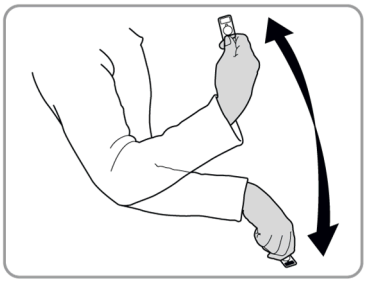
SAYANA® PRESS is a white to off-white suspension in a single dose container for subcutaneous injection. The container contains 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL.

SAYANA® PRESS is supplied as single dose container in a foil pouch (carton box of 200's).

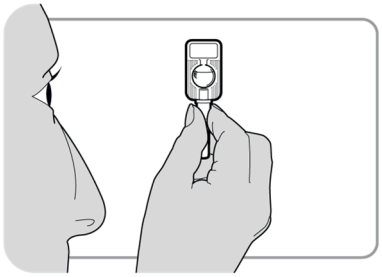
6.6 Special precautions for disposal and other handling

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.

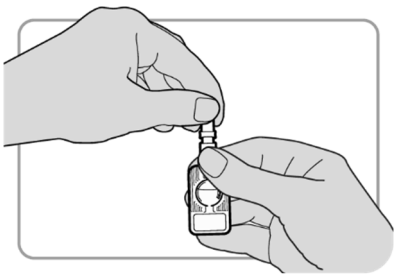


- The medicine should appear white and uniform. If it is not, discard the injector and use a new one.
- If you see liquid leaking out or any other problem, discard the injector and use a new one.
- If there is a delay before injecting, you must repeat the mixing step.

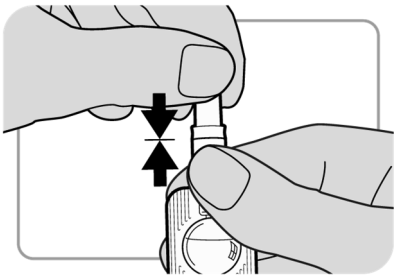


Activating the injector

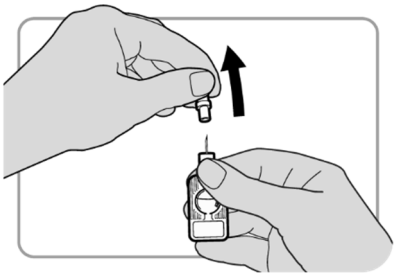
- Hold the injector firmly by the port, making sure the needle shield is pointing upwards. Take care not to squeeze the reservoir.
- Hold the needle shield with the other hand.



- 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.



7. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pfizer Manufacturing Belgium NV, Rijksweg 12, B-2870 Puurs, Belgium

Secondary packed by and imported by:
PT. Pfizer Indonesia Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER

Reg. No.: DKI2086101843A1

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

03/2020

CDS version 24