SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SAYANA® 104 mg/0,65 mL aqueous suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,65 mL contains 104 mg medroxyprogesterone acetate.

Sugar free.

Excipients with known effect

Preservatives

Each 0,65 mL of suspension contains 1,04 mg methyl parahydroxybenzoate.

Each 0,65 mL of suspension contains 0,0975 mg propyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection

White to off white homogenous suspension when mixed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Contraception
- Management of endometriosis-associated pain

4.2 Posology and method of administration

Posology

Contraception

The recommended dose is a pre-filled injection of 104 mg given subcutaneously, once every 3 months.

First injection

The first 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 breastfeeding, at or after 6 weeks postpartum.

Second and subsequent injections

The second and subsequent injections should be given at 3-month intervals (12 – 14 weeks). If more than 14 weeks have elapsed since the last subcutaneous injection, pregnancy should be ruled out before administering the next subcutaneous injection.

Self-injection

When used for contraception, SAYANA Pre-filled injection (pre-filled single use injection system) may be administered by a health care provider or, when considered appropriate by the health care provider, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance. The self-injection option is not recommended for the SAYANA Pre-filled syringe presentation or when SAYANA is used for management of endometriosis-associated pain.

Administration of SAYANA should be initiated under the supervision of a health care provider. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA Pre-filled injection if their health care provider determines that it is appropriate and with medical follow-up as necessary. See section 4.2 - *Instructions for use*, for full details on preparing and giving an injection.

Switching from other methods of contraception

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

Endometriosis

A pre-filled injection of 104 mg given subcutaneously by a health care provider every 3 months for at least 6 months.

Special populations

Hepatic insufficiency

The effect of hepatic disease on the pharmacokinetics of SAYANA is unknown. However, SAYANA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

Renal insufficiency

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

Paediatric population

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for intramuscular administration of medroxyprogesterone acetate (see section 4.4). Other than concerns about loss of bone mineral density (BMD), the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Method of administration

For subcutaneous injection.

SAYANA must be administered as a subcutaneous injection into the anterior thigh or abdomen. SAYANA subcutaneous suspension is not for intramuscular use. Dosage does not need to be adjusted for body weight.

The sterile aqueous suspension of SAYANA should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension**.** Once opened: use immediately, discard any unused portion.

The detailed instructions on the injection procedure provided below should be followed.

Instructions for use

Preparing and giving an injection with SAYANA Pre-filled injection

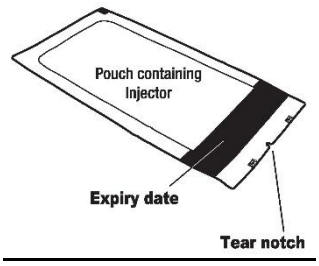
SAYANA Pre-filled injection can be given by a health care provider or the patient.

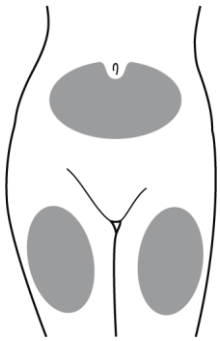
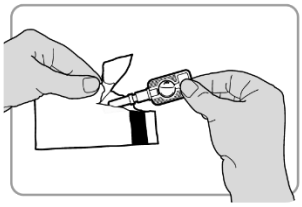
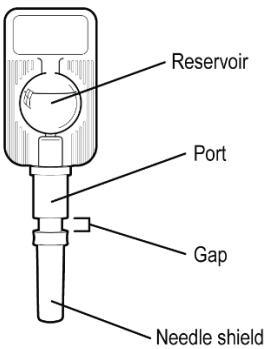
Introduction

SAYANA Pre-filled injection is a disposable injector that contains a single dose of medicine sealed in a reservoir. These instructions show step-by-step how to prepare and give the injection.

SAYANA Pre-filled injection 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 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 medicine should be injected slowly for 5-7 seconds.

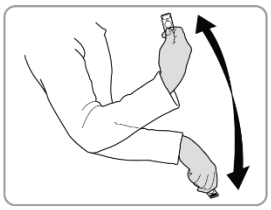
SAYANA Pre-filled injection

Step 1. Getting ready **You will need** – A SAYANA injector (in its sealed foil pouch). – A suitable container for the used injector. – A clean cotton pad or clean paper tissue.	

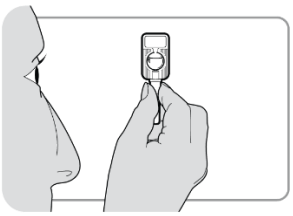
• Wash and dry your hands thoroughly before starting. • Check that the pouch does not appear to be damaged. • Check that the expiry date has not passed. • Ensure the pouch is at room temperature.	
Step 2. Selecting an injection area • Choose a suitable area for the injection, either the abdomen or the front upper thigh. Avoid bony areas and the navel (belly button). • The area of skin must be free from scars and skin conditions such as eczema or psoriasis. • Change the site with each injection • Clean the area of skin as your health care provider has told you.	
Step 3. Preparing the injector • Carefully tear open the foil pouch at the tear notch. • Take out the injector. Do not remove the needle shield from the injector yet. • Check the injector. There should be a gap between the needle shield and the port. • Discard the injector and use a new one if: – There is no gap. – The injector is damaged. – The needle shield has come off or is missing.	 

Step 4. Mixing the medicine

- Hold the injector firmly by the port.
- Shake the injector vigorously for at least 30 seconds to mix the medicine.

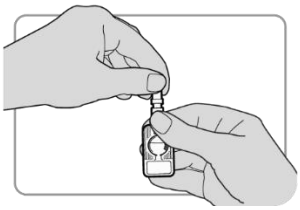


- The medicine should appear white and uniform. If it is not, discard the injector and use a new one.
- If you see liquid leaking out or any other problem, discard the injector and use a new one.
- If there is a delay before injecting, you must repeat the mixing step.

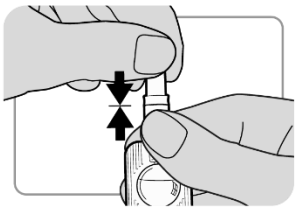


Step 5. Activating the injector

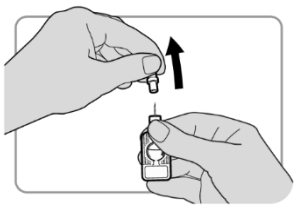
- Hold the injector firmly by the port, making sure the needle shield is pointing upwards. Take care not to squeeze the reservoir.



- 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.

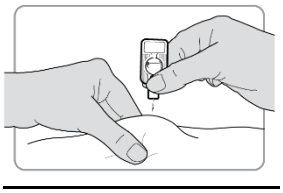


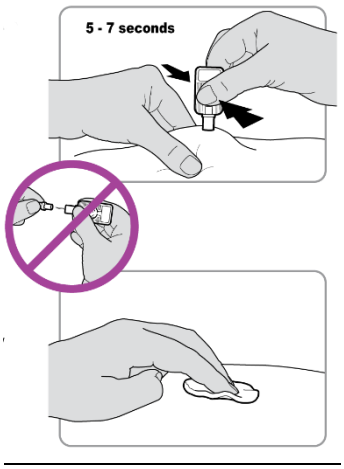
- Pull the needle shield off and discard it.

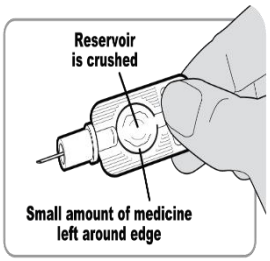


Step 6. Injecting the dose

- Gently pinch a large area of skin. Keep the skin pinched all through this step.
- Hold the injector by the port with the needle pointing straight downwards.
- Insert the needle into the skin so that the port just touches the skin.
- Squeeze the reservoir slowly to inject the medicine. You should take about **5-7 seconds** to do this.
- Gently pull the needle out of the skin. Let go of the skin.
- Check whether any medicine has leaked out of the injector or has appeared on the skin.
- **Do not replace the needle shield.**
- Use a clean cotton pad to press lightly on the injection area for a few seconds. Do not rub the area.





Important advice • After the injection a small amount of medicine will be left around the inside edge of the reservoir. This is normal. • However, if any medicine has leaked out of the injector or appeared on the skin, then a problem may have occurred. • **If you believe for any reason that the full dose has not been given, speak to your health care provider about alternative methods of contraception until the next scheduled injection.** • **Do not inject an additional dose.** **After injection care:** • If you get any symptoms of allergic reaction (see section 4.8) seek medical help immediately. • Monitor the appearance of the injection site until the next injection. If you notice any skin indentation or dimpling at the injection site, tell your health care provider.	
Step 7. Disposing of the injector • Immediately dispose of the used injector into a suitable container in accordance with your local authority requirements or as you have been told by your health care provider. • The injector is for a single injection only and must not be re-used.	

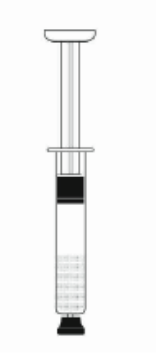
Step 8. Record the date of your injection and should you wish to continue, calculate the date of your next scheduled injection of SAYANA.	Date _____
Retain this leaflet for your records.	Date of Next Injection (*add 3 months*) _____

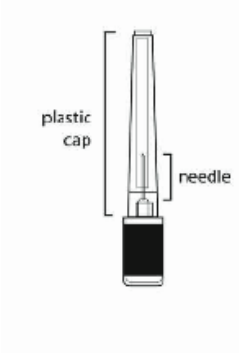
SAYANA® Pre-filled syringe

SAYANA Pre-filled syringe is supplied in a pre-filled single use syringe system.

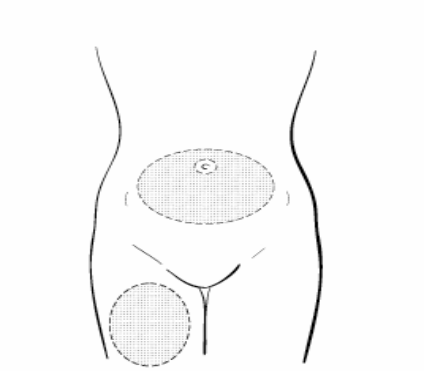
Getting ready

Ensure that the medication is at room temperature. Make sure the following components are available.

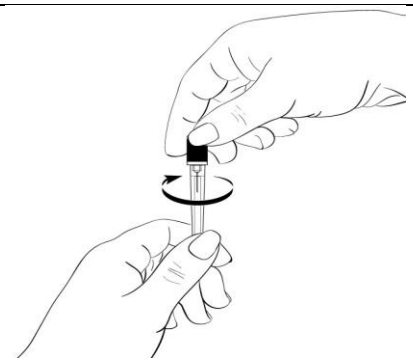
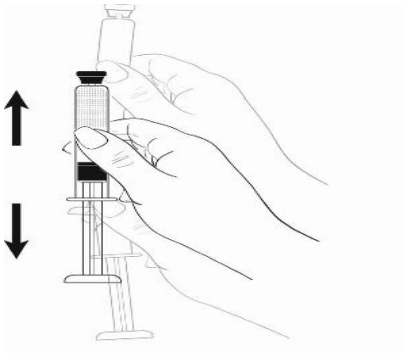




Inspect the injection visually for particulate matter and discoloration prior to administration.

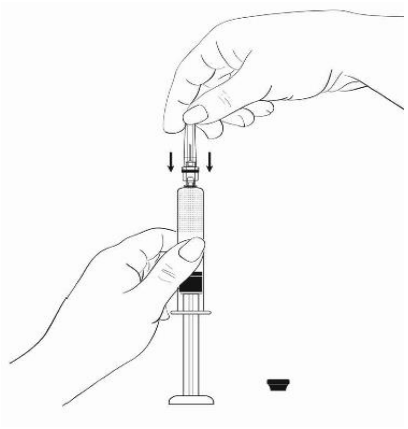
<table>
<tr><td colspan="2">STEP 1: CHOOSING AND PREPARING THE INJECTION AREA</td></tr>
<tr><td>Choose the injection area.
• Avoid boney areas and the umbilicus
• The upper thigh & abdomen are preferred injection sites. See shaded areas in diagram
Use an alcohol pad to wipe the skin in the injection area you have chosen.
• Allow the skin to dry</td><td>Preferred injection areas:
  </td></tr>
<tr><td colspan="2">STEP 2: SYRINGE PREPARATION</td></tr>
<tr><td>Gently twist off the protective end cap from the needle to break the seal. Set aside.

Hold the syringe firmly by the barrel, with the barrel pointing upward.
• Shake it forcefully for at least 1 minute to thoroughly mix the medication

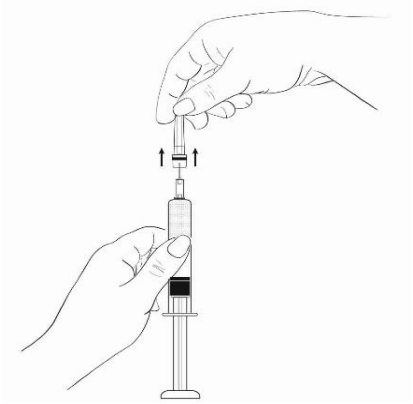
Hold the syringe barrel firmly.
• Unscrew the protective cap from the tip of the syringe barrel</td><td> 
 
  </td></tr>
</table>

Hold the syringe barrel firmly.

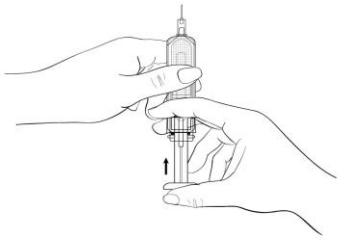
- Attach the needle to the barrel of the syringe by pushing down firmly with a slight twist



- While holding the syringe barrel firmly, **remove the plastic cover** from the needle without twisting, ensuring the needle is still firmly attached to the syringe.

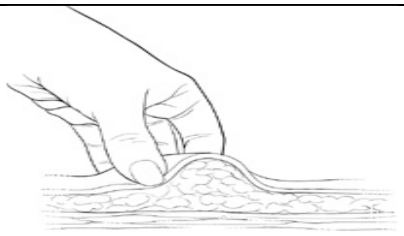


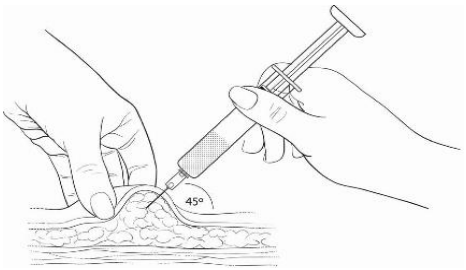
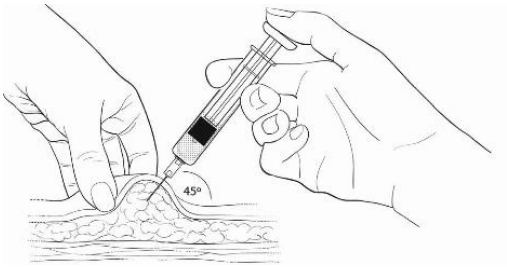
- While holding the syringe with needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe. There should be no air within the barrel.



STEP 3: INJECTING THE DOSE

Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and forefinger, pulling it away from the body.



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 **Inject the medication** slowly until the syringe is empty. • It is important that the entire dose of SAYANA is given • This should take about 5 - 7 seconds • Use a clean cotton pad to **press lightly on the injection area** for a few seconds. • **Do NOT rub the area**	 
STEP 4: DISPOSING THE NEEDLE AND SYRINGE	
• After administration of the dose, dispose of the used injection system in a safe and proper manner, according to local guidance for disposal of sharps. • The injection system is for a single injection only. It should NEVER be reused.	

4.3 Contraindications

- Known hypersensitivity to medroxyprogesterone acetate or to any of the excipients of SAYANA (listed in section 6.1)
- Known or suspected pregnancy and lactation (see section 4.6)
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known or suspected malignancy of the breast
- Thrombophlebitis or a history of thrombophlebitis

4.4 Special warnings and precautions for use

Loss of bone mineral density (BMD)

Use of SAYANA reduces serum ~~o~~estrogen levels in premenopausal women and is associated with significant loss of BMD as bone metabolism accommodates to a lower ~~o~~estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life.

Since loss of (BMD) may occur in pre-menopausal women who use SAYANA 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.

SAYANA should be used as a long-term (e.g., longer than 2 years) birth control method or endometrial treatment only if other birth control methods or endometrial treatments are inadequate. BMD should be evaluated when a female needs to continue use of SAYANA long term.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SAYANA in woman with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of medicines that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis

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

BMD changes in adult women

A controlled, clinical study of adult women using medroxyprogesterone acetate intramuscular injectable suspension 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 –2,86 %, -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. After stopping treatment, there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. BMD increased but deficits at the total hip, femoral neck and lumbar spine remained. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SAYANA 104 mg subcutaneously with women using medroxyprogesterone acetate intramuscular injectable suspension 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment.

Bleeding irregularities

Most women using SAYANA experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding or spotting, heavy or continuous bleeding). Patients should be appropriately counselled concerning the likelihood of menstrual disturbance. As women continue using SAYANA, fewer experience irregular bleeding and more experience amenorrhoea. If abnormal bleeding associated with SAYANA persists or is severe, appropriate investigation and treatment should be instituted. Unexpected vaginal bleeding should be investigated.

Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of SAYANA. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance.

In cases of breakthrough bleeding, organic causes should be excluded. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

The use of SAYANA may mask the onset of the climacteric.

Thromboembolic disorders

A patient who develops a thrombotic or thromboembolic event, e.g., pulmonary embolism, cerebrovascular disease, retinal thrombosis or deep venous thrombosis, while undergoing therapy with medroxyprogesterone containing medicines such as SAYANA should not be re-administered SAYANA. Women with a prior history of thromboembolic disorders should not receive SAYANA.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have been reported in patients treated with SAYANA.

Ocular disorders

In any patient who develops an acute impairment of vision, proptosis, diplopia, or migraine headache, SAYANA should be discontinued and the patient carefully evaluated ophthalmologically to exclude the presence of papilloedema or retinal vascular lesions before continuing treatment.

Fluid retention

SAYANA may cause fluid retention; therefore, caution should be exercised in treating any patient with a pre-existing condition that might be adversely affected by fluid retention, such as epilepsy, migraine, asthma or cardiac or renal dysfunction.

Central nervous system disorders

Mood changes and depression are side effects reported with the use of hormonal contraceptives including SAYANA. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with SAYANA.

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SAYANA.

Carbohydrate metabolism

Some patients receiving SAYANA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving SAYANA.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

Effects on laboratory tests

The pathologist (laboratory) should be informed of the patient's use of SAYANA if endometrial or endocervical tissue is submitted for examination.

The medical practitioner/laboratory should be informed that use of SAYANA may decrease the levels of the following endocrine biomarkers:

- Plasma/urinary steroids (e.g., cortisol, ~~o~~estrogen, pregnanediol, progesterone, testosterone)
- Plasma/urinary gonadotrophins (e.g., LH and FSH)
- Sex-hormone-binding-globulin

Liver function

Liver function tests may be affected by treatment with SAYANA. Therefore, if such tests are abnormal in a patient taking SAYANA, it is recommended that they be repeated after SAYANA has been withdrawn.

If jaundice develops, consideration should be given to not re-administer SAYANA.

Weight changes

Weight gain may be associated with the use of SAYANA.

Cancer risks

Long-term case-controlled surveillance of users of medroxyprogesterone acetate intramuscular injectable suspension for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer.

Sexually transmitted infections

Patients should be counselled that SAYANA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SAYANA 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.

Paediatric population

BMD changes in adolescent females (12 – 18 years) after long-term treatment for contraception

An open-label clinical study of medroxyprogesterone acetate injectable suspension (150 mg intramuscularly every 3 months for up to 240 weeks) in adolescent females (12 – 18 years) for contraception showed a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was -2,1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6,4 % and -5,4 % respectively. In general, adolescents increase bone density during the period of growth following menarche. Post-treatment follow-up showed that lumbar spine recovered to baseline levels approximately 1,2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4,6 years after treatment was discontinued.

Preservative sensitivity

SAYANA contains the excipients methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm. If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with SAYANA.

SAYANA is metabolised *in vitro* primarily by hydroxylation via cytochrome P450 3A4 (CYP3A4). Specific interaction studies evaluating the clinical effects of CYP3A4 inducers or inhibitors on SAYANA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other medicines.

The clearance of SAYANA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that medicines which induce hepatic enzymes will significantly affect kinetics of SAYANA. Therefore, no dose adjustment is recommended in patients receiving medicines known to affect hepatic metabolising enzymes.

Aminoglutethimide administered concomitantly with SAYANA may significantly depress the bioavailability of SAYANA.

4.6 Fertility, pregnancy and lactation

Pregnancy

SAYANA is contraindicated in women who are pregnant.

Reports suggest an association between intra-uterine exposure to progestational medicines in the first trimester of pregnancy and genital abnormalities in male and female foetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection with SAYANA 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 SAYANA are uncommon.

If the patient becomes pregnant while using SAYANA, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

Safety in breastfeeding has not been established. SAYANA and its metabolites are excreted in breast milk and mothers receiving SAYANA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

The effect of SAYANA on the ability to drive and use machinery has not been systematically evaluated. Dizziness is a potential side effect. Patients should be aware of how they might be affected by SAYANA before driving or operating machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Side effects reported during safety and efficacy studies have been classified 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); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Contraception

Adverse reactions reported by 5 % or more of all women in clinical trials of SAYANA for contraception included headache (9 %), metrorrhagia (7 %), increased weight (7 %), amenorrhea (6 %) and injection site reactions (6 %).

System organ class	**Frequency**	**Adverse events**
Metabolism and nutrition disorders	Very common	Increased weight
	Uncommon	Decreased weight, increased appetite, fluid retention, decreased appetite
Psychiatric disorders	Common	Depression, decreased libido, affective disorder, anxiety, insomnia, irritability
	Uncommon	Anorgasmia, emotional disorder

Nervous system disorders	Common	Headache, dizziness, migraine
Ear and labyrinth disorders	Uncommon	Vertigo
Vascular disorders	Uncommon	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Abdominal distension
Skin and subcutaneous tissue disorders	Common	Acne, dermatitis
	Uncommon	Hirsutism, chloasma, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Common	Back pain, pain in extremity
	Uncommon	Muscle spasms
Reproductive system and breast disorders	Common	Amenorrhoea, breast pain, metrorrhagia, menometrorrhagia, menorrhagia, dysmenorrhoea, vaginitis
	Uncommon	Breast tenderness, vaginal discharge, vulvovaginal dryness, breast enlargement, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome
General disorders and administration site conditions	Common	Fatigue, injection site reaction
Investigations	Common	Abnormal smear cervix
	Uncommon	Abnormal hepatic enzyme

Please note that in patients taking medroxyprogesterone acetate injection (150 mg intramuscular), there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures.

Adverse events reported during contraception post-marketing experience

System Organ Class	**Adverse events**
Immune system disorders	Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, angioedema
Skin and subcutaneous tissue disorders	Acquired lipodystrophy
General disorders and administration site conditions	Injection site pain/tenderness, injection site persistent atrophy/indentation/dimpling, injection site nodule/lump

Endometriosis-associated pain

System organ class	**Frequency**	**Adverse events**
Metabolism and nutrition disorders	Very common	Increased weight
	Not known	Decreased weight
Psychiatric disorders	Common	Anxiety, depression, insomnia, irritability, decreased libido, affective disorder
Nervous system disorders	Very common	Headache
	Common	Dizziness, formication, hypersomnia, migraine
	Uncommon	Paraesthesia
Cardiac disorders	Uncommon	Palpitations
Vascular disorders	Common	Hot flush
Gastrointestinal disorders	Very common	Nausea
	Common	Abdominal distention
Skin and subcutaneous tissue disorders	Common	Acne, alopecia, dermatitis

Musculoskeletal and connective tissue disorders	Common	Arthralgia, pain in extremity
	Uncommon	Polyarthralgia
Reproductive system and breast disorders	Very common	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), metrorrhagia
	Common	Breast pain, breast tenderness, vaginitis, menorrhagia, pelvic pain, vulvovaginal dryness
	Uncommon	Galactorrhoea, ovarian cyst
General disorders and administration site conditions	Common	Fatigue

Adverse events reported during endometriosis post-marketing experience

System Organ Class	**Adverse events**
Immune system disorders	Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, angioedema
Skin and subcutaneous tissue disorders	Acquired lipodystrophy
General disorders and administration site conditions	Injection site reaction, injection site pain/tenderness, injection site persistent atrophy/indentation/dimpling, injection site nodule/lump

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterone with or without ~~o~~estrogens

Medroxyprogesterone acetate is a synthetic analogue of 17α- hydroxyprogesterone with anti-~~o~~estrogenic, anti-androgenic and anti-gonadotrophic effects.

Medroxyprogesterone acetate inhibits the secretion of gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH)] from the anterior pituitary which, in turn, prevents follicle maturation and ovulation and causes thickening of cervical mucous which inhibits sperm entry into the uterus.

Suppression of serum ~~o~~estradiol concentrations and a possible direct action of medroxyprogesterone acetate on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous injection, the mean T_{max} is attained approximately one week after injection. The peak medroxyprogesterone acetate 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 subcutaneous injection.

Effect of injection site

Medroxyprogesterone acetate subcutaneous was administered into the anterior thigh or the abdomen to evaluate effects on medroxyprogesterone acetate concentration-time profile. Medroxyprogesterone acetate 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 medroxyprogesterone acetate averages 86 %. Medroxyprogesterone acetate binding occurs primarily to serum albumin; no binding of medroxyprogesterone acetate occurs with sex hormone-binding globulin (SHBG).

Metabolism

Medroxyprogesterone acetate is extensively metabolised in the liver by cytochrome P450 enzymes.

Elimination

Residual medroxyprogesterone acetate concentrations at the end of the dosing interval (3 months) of medroxyprogesterone acetate subcutaneous injection are generally below 0,5 ng/mL, consistent with its apparent terminal half-life of ≈approximately 40 days after subcutaneous administration. Most medroxyprogesterone acetate metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulphates.

Special populations

Race

There were no apparent differences in the pharmacokinetics and/or dynamics of medroxyprogesterone acetate after subcutaneous administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 medroxyprogesterone acetate trough (C_{min}) concentrations and the half-lives were comparable for the three BMI groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Sodium chloride

Macrogol (polyethylene glycol) 3350

Polysorbate 80

Monobasic sodium phosphate · 1 H_2O

Disodium phosphate dodecahydrate

Methionine

Povidone

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

SAYANA Pre-filled injection

24 months

SAYANA Pre-filled syringe

36 months

6.4 Special precautions for storage

- Store at or below 25 °C and protect from light.
- Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA Pre-filled injection

A single 1 mL pre-filled multilayered thermoformed plastic film reservoir, affixed with a single-use 23-gauge needle, packed in a foil laminate pouch (single pack) or in a box containing 200 single pre-filled clear plastic reservoirs with needles in a foil pouch.

SAYANA Pre-filled syringe

A single 2,25 mL glass syringe with a fluoro coated bromobutyl rubber plunger stopper and bromobutyl rubber tip cap assembled with a plunger rod. The assembled syringe is packed in a tray and the needle is included in the package. The tray is sealed with a foil. Tray and printed materials are packaged in a carton. Single pack is for single use only.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

SAYANA Pre-filled injection and Pre-filled syringe are for single use only.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

45/21.8.2/1139

9. DATE OF FIRST AUTHORISATION

26 June 2019

10. DATE OF REVISION OF THE TEXT

12 April 2024