Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

SAYANA 104MG/0.65ML SUSPENSION FOR INJECTION

UK/H/0960/001/MR
UK licence no: PL 00057/0589

Pfizer Limited

SAYANA 104MG/0.65ML SUSPENSION FOR INJECTION

LAY SUMMARY

On 9th July 2007, Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, The Netherlands, Norway and Poland granted Marketing Authorisations to Pfizer Limited for the medicinal product Sayana 104mg/0.65ml Suspension for Injection. The licences were granted by Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). A licence had previously been granted in the UK on 26th October 2005.

Sayana 104mg/0.65ml Suspension for Injection can be used:

- For long-term contraception, as decided by the patient and the healthcare provider. However, use for longer than 2 years is only after re-evaluation of the risks versus benefits by the healthcare provider to make sure that it is still the best option.
- In teenagers only after other methods of contraception have been discussed with the healthcare provider and considered unsuitable or unacceptable.

The active ingredient in Sayana 104mg/0.65ml Suspension for Injection, medroxyprogesteroneacetate, is similar to the natural hormone progesterone that is produced in ovaries during the second half of a menstrual cycle. It acts by preventing eggs from fully developing and being released from the ovaries during the menstrual cycle. This prevents fertilisation by sperm and thus pregnancy.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Sayana 104mg/0.65ml Suspension for Injection outweigh the risks. Hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Sayana 104mg/0.65ml Suspension for Injection
Type of Application	Full dossier, Article 8.3
Active Substance	Medroxyprogesterone acetate
Form	Suspension for injection
Strength	104mg/0.65ml
MA Holder	Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, Kent, UK
RMS	UK
CMS	Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, The Netherlands, Norway and Poland
Procedure Number	UK/H/0960/001/MR
Timetable	Day 90 – 9th July 2007

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

SAYANA®104 mg/0.65 mL suspension for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA single dose pre-filled syringe containing 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection.

Excipients:
Methyl parahydroxybenzoate – 1.04 mg
Propyl parahydroxybenzoate – 0.0975 mg
Sodium – 2.47 mg

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

Since loss of bone mineral density (BMD) may occur in females of all ages who use SAYANA long-term (see section 4.4 Special Warnings and Precautions for Use), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Use in Adolescents (12-18 years)
In adolescents, use of SAYANA is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with SAYANA during the critical period of bone accretion (see section 4.4)

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

4.2 Posology and method of administration

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

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

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

Post Partum: To increase assurance that the patient is not pregnant at the time of first administration, this injection should be given within 5 days post partum if not breast-feeding.

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

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Loss of Bone Mineral Density:
Use of SAYANA 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 SAYANA 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 SAYANA by younger women will reduce peak bone mass and increase the risk for fracture in later life.

A study to assess the BMD effects of medroxyprogesterone acetate IM (Depo-Provera, DMPA) in adolescent females showed that its use was associated with a significant decline in BMD from baseline. In the small number of women who were followed-up, mean BMD recovered to around baseline values by 1- 3 years after discontinuing treatment. In adolescents, SAYANA may be used, but only after other methods of contraception have been discussed with the patients and considered to be unsuitable or unacceptable.

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

Significant risk factors for osteoporosis include:

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

A retrospective cohort study using data from the General Practice Research Database (GPRD) reported that women using MPA injections (DMPA), have a higher risk of fracture compared with contraceptive users with no recorded use of DMPA (incident rate ratio 1.41, 95% CI 1.35-1.47 for the five year follow-up period); it is not known if this is due to DMPA, or to other related lifestyle factors which have a bearing on fracture rate. By contrast, in women using DMPA, the fracture risk before and after starting DMPA was not increased (relative risk 1.08, 95% CI 0.92-1.26). Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life.

For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to section 5.1 (Pharmacodynamic Properties). Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Menstrual Irregularities:
Most women using SAYANA experienced alteration of menstrual bleeding patterns. Patients should be appropriately counseled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. As women continued using SAYANA, fewer experienced irregular bleeding and more experienced amenorrhea. After receiving the fourth dose, 39% of women experienced amenorrhea during month 6. During month twelve, 56.5% of women experienced amenorrhea. The changes in menstrual patterns from the three contraception trials are presented in Figures 1 and 2. Figure 1 shows the increase in the percentage of women experiencing amenorrhea over the 12 month study. Figure 2 presents the percentage of women experiencing spotting only, bleeding only, and bleeding and spotting over the same time period. In addition to amenorrhea, altered bleeding patterns included intermenstrual bleeding, menorrhagia and metrorrhagia. If abnormal bleeding associated with SAYANA persists or is severe, appropriate investigation and treatment should be instituted.

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

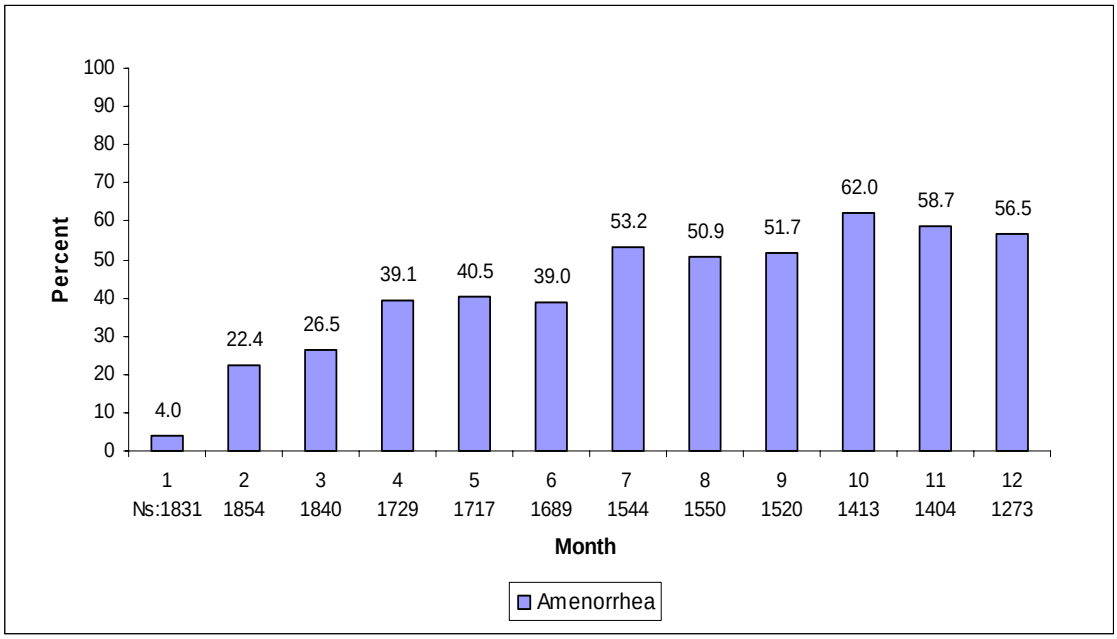
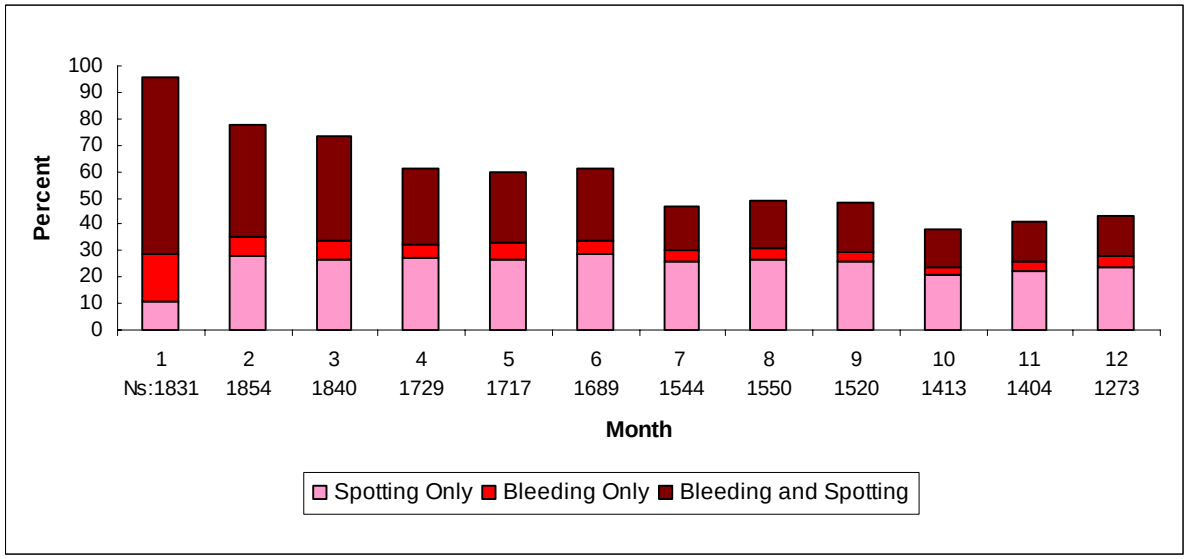


Figure 2. Percent of SAYANA -Treated Women with Bleeding and/or Spotting per 30-Day Month Contraception Studies (ITT Population, N=2053)



Cancer Risks:
Long-term case-controlled surveillance of DMPA-IM 150 mg users found no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users. A meta-analysis in 1996 from 54 epidemiological studies reported that there is a slight increased relative risk of having breast cancer diagnosed in women who are currently using hormonal contraceptives. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in hormonal contraceptive users, biological effects or a combination of both. The additional breast cancers diagnosed in current users of hormonal contraceptives or in women who have used them in the last ten years are more likely to be localised to the breast than those in women who never used hormonal contraceptives.

Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives. In the meta-analysis the results for injectable progestogens (1.5% of the data) and progestogen only pills (0.8% of the data) did not reach significance although there was no evidence that they differed from other hormonal contraceptives. Whilst the background risk of breast cancer increases with age, the excess number of breast cancer diagnoses in current and recent injectable progestogen (IP) users is small in relation to the overall risk of breast cancer, possibly of similar magnitude to that associated with combined oral contraceptives. However, for IPs, the evidence is based on much smaller populations of users (less than 1.5% of the data) and is less conclusive than for combined oral contraceptives. It is not possible to infer from these data whether it is due to an earlier diagnosis of breast cancer in ever-users, the biological effects of hormonal contraceptives, or a combination of reasons.

The most important risk factor for breast cancer in IP users is the age women discontinue the IP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping IP use, such that by 10 years there appears to be no excess.

The evidence suggests that compared with never-users, among 10,000 women who use IPs for up to 5 years but stop by age 20, there would be much less than 1 extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years of use of the IP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years of use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed against the known benefits.

Thromboembolic Disorders
Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops such an event, e.g. pulmonary embolism, cerebrovascular disease, retinal thrombosis or deep venous thrombosis, while undergoing therapy with SAYANA should not be 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 use in this population.

Anaphylaxis and Anaphylactoid Reaction
If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

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

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

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

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

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

Protection Against Sexually Transmitted Diseases
Patients should be counselled that SAYANA does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

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

Liver Function
If jaundice develops in any woman receiving SAYANA, consideration should be given to not re-administer the medication. (See section 4.3)

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 methylparahydroxbenzote and propylparahydroxbenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

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

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with SAYANA.
Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

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

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

One study found that infants from unintentional pregnancies that occurred 1 to 2 months after injection of medroxyprogesterone acetate Injection 150 mg IM 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 medroxyprogesterone acetate Injection 150 mg IM 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.

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with medroxyprogesterone acetate injection 150 mg IM, 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.

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

4.8 Undesirable effects
In three large clinical trials involving 1980 women who were treated with SAYANA for up to 1 year, the following adverse events were reported as drug related. Adverse reactions are listed according to the following categories. These are as follows:
Very Common >10%
Common ≥1% and < 10%
Uncommon >0.1% and <1%
Not known (cannot be estimated from the available data)

<u>Ear and Labyrinth Disorders</u>
Uncommon: Vertigo

<u>Gastrointestinal Disorders</u>
Common: Abdominal pain
Uncommon: Abdominal distension, nausea

Infection & Infestations
Uncommon: Vaginitis

Metabolism & Nutrition Disorders
Very Common: Weight increase, weight decrease
Uncommon: Appetite decrease, appetite increase, fluid retention

Musculoskeletal, Connective Tissue & Bone Disorders
Uncommon: Back pain, muscle cramps, pain in limbs
Frequency not known: Arthralgia, Osteoporosis including oesteoporotic fractures, loss of bone mineral density

Nervous System Disorders
Common: Headache
Uncommon: Dizziness, migraine
Frequency not known: Convulsions, somnolence

Reproductive System & Breast Disorders
Common: Amenorrhea, breast pain/tenderness, intermenstrual bleeding, menometrorrhagia, menorrhagia
Uncommon: Vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome
Frequency not known: Abnormal uterine bleeding (irregular, increase, decrease), galactorrhea

Vascular Disorders
Uncommon: Hot flushes, hypertension, varicose veins, thrombophlebitis, pulmonary embolus
Frequency not known: Thromboembolic disorders

Cardiovascular Disorders
Frequency not known: Tachycardia

Immune System Disorders
Frequency not known: Hypersensitivity reactions (e.g. anaphylaxis & anaphylactoid reactions, angioedema)

Hepato-biliary disorders
Uncommon: Abnormal liver enzymes
Frequency not known: Jaundice, disturbed liver function

Skin & Subcutaneous Tissue Disorders
Common: Acne
Uncommon: Chloasma, dermatitis, ecchymosis, rash, alopecia, hirsutism
Frequency not known: Pruritus, urticaria, skin striae

General Disorders and Administration Site Conditions
Common: Fatigue, injection site reactions
Frequency not known: Asthenia, pyrexia

Investigations
Uncommon: Cervical smear abnormal
Frequency not known: Decreased glucose tolerance

Psychiatric Disorders
Common: Anorgasmia, depression, emotional disturbance, libido decreased, mood disorder, irritability
Uncommon: Anxiety, insomnia
Frequency not known: Nervousness

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.

SAYANA MPA injectable suspension inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation. The primary mechanism of ovulation suppression also results in endometrial thinning, and these actions produce its contraceptive effect.

BMD Changes in Adult Women

A study comparing changes in BMD in women using SAYANA with women using medroxyprogesterone acetate injection (150 mg IM) showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SAYANA group are listed in Table 1.

Table 1. Mean Percent Change from Baseline in BMD in Women Using SAYANA 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)

In another controlled, clinical study adult women using medroxyprogesterone acetate injection (150 mg 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 –2.86%, -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. Please refer to Table 2 below for further details.

After stopping use of medroxyprogesterone acetate injection (150 mg 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.

Table 2. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort after 5 Years of Therapy with Medroxyprogesterone acetate 150 mg IM and after 2 Years Post-Therapy or 7 Years of Observation (Control)

Time in Study	Spine		Total Hip		Femoral Neck	
	Medroxyprogesterone acetate	Control	Medroxyprogesterone acetate	Control	Medroxyprogesterone acetate	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received medroxyprogesterone acetate injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received medroxyprogesterone acetate Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

BMD Changes in Adolescent Females (12-18 years)

Results from an open-label, non-randomised, clinical study of medroxyprogesterone acetate Injection (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. Post-treatment follow-up showed that, based on mean values, lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and that hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued. 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 (n=71 at 60 weeks and n=25 at 240 weeks after treatment discontinuation). 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.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of MPA following a single SC injection of SAYANA are shown in Table 1.

Table 1. Pharmacokinetic Parameters of MPA After a Single SC Injection of SAYANA in Healthy Women (n = 42)

	C_{max} (ng/mL)	T_{max} (day)	$C_{91\ (min)}$ (ng/mL)	AUC_{0-91} (ng·day/mL)	$AUC_{0-\infty}$ (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/mL after a single SC injection.

Effect of Injection Site

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

Race

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

Effect of Body Weight

No dosage adjustment of SAYANA is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n = 42, body mass index [BMI] ranged from 18.2 to 46.0 kg/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 13 week dosing interval.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. 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

3 years

6.4 Special precautions for storage

Do not refrigerate or freeze

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent

CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00057/0589

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/10/2005

10 DATE OF REVISION OF THE TEXT
15/01/2010

Module 3
Product Information Leaflet

PACKAGE INFORMATION LEAFLET

SAYANA®

104 mg/0.65 mL suspension for injection

MEDROXYPROGESTERONE ACETATE

5R7631
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Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What SAYANA is and what it is used for

SAYANA is a contraceptive. It can be used:
- For long-term contraception where you and the person who provides your contraception (e.g. your doctor, nurse or healthcare provider) have decided that this method is the most suitable for you. However, if you wish to use SAYANA for more than 2 years, your health professional/doctor/nurse may wish to re evaluate the risks and benefits of using SAYANA to make sure that it is still the best option for you.
- By teenagers, but only after other methods of contraception have been discussed with the person who provides your contraception and are considered unsuitable or unacceptable.

The active ingredient in SAYANA, medroxyprogesterone acetate (MPA), is similar to (but not the same as) the natural hormone progesterone that is produced in the ovaries during the second half of your menstrual cycle. SAYANA acts by preventing an egg from fully developing and being released from the ovaries during your menstrual cycle. If an egg is not released it cannot become fertilised by sperm and result in pregnancy.

2. Before you use SAYANA

Do not use SAYANA

- If you are allergic (hypersensitive) to medroxyprogesterone acetate (MPA) or any of the other ingredients of SAYANA
- If you think you may be pregnant
- If you have unexplained vaginal bleeding
- If you have liver disease
- If you have had or think you have cancer of the breast or sex organs
- If you have a blood clot in a vein in your leg (a "deep vein thrombosis") or a blood clot that has travelled to your lung or another part of your body (an "embolus")
- If you have problems with your circulation (e.g. pains in your legs or chest when you walk), or with your blood clotting too easily ('thrombosis' or 'embolism')
- If you have problems due to the metabolism of your bones
- If you have or have had a disease affecting the blood vessels of the brain

Take special care with SAYANA

Before your doctor prescribes SAYANA, you may need to have a physical examination.
It is important to tell your doctor if you have, or have had in the past, any of the following conditions.
Your doctor will then discuss with you whether SAYANA is suitable for you.

Tell your doctor if you have:

- Migraine headaches
- Diabetes or a family history of diabetes
- Severe pain or swelling in the calf (indicating a possible clot in the leg, which may be called phlebitis)
- A blood clot in the lung (pulmonary embolism)
- A blood clot in your eye affecting your vision (retinal thrombosis)
- A history of heart disease or cholesterol problems including any family history
- If you have recently had a "hydatidiform mole" which is a type of abnormal pregnancy
- Past history of depression
- Irregular, light, or heavy menstrual periods
- An unusual breast x-ray, fibrocystic breast disease, breast nodules or lumps, or bleeding from your nipples
- Had a stroke
- Family history of breast cancer
- Kidney disease
- High blood pressure
- Asthma

- Epilepsy.

Protection against sexually transmitted diseases
SAYANA does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a pescription. There are some medicines that may interact with SAYANA, which include medicines that thin your blood (anticoagulants).

Medicines can sometimes interfere with each other. If you receive treatment from any other doctor, nurse or qualified healthcare professional make sure they are aware that you are using SAYANA as a contraceptive.

Pregnancy and breastfeeding
Do not take SAYANA if you are pregnant. If you think you may have become pregnant while using SAYANA tell your doctor immediately.

SAYANA can be passed to the nursing infant in the breast milk, however no harmful effects have been found in children.

Always ask your doctor, nurse, or healthcare professional for advice before taking any medicine.

Driving and using machines
No effects on the ability to drive or use machines have been seen with SAYANA.

Important information about some of the ingredients of SAYANA
SAYANA also contains the following two ingredients: methyl parahydroxybenzoate (E218) & propyl parahydroxybenzoate (E216). These may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol sodium (23 mg) per 104 mg/0.65 mL, i.e. essentially 'sodium-free'.

3. How to use SAYANA

Method and route of administration
SAYANA is injected under the skin into the front upper thigh or abdomen. The injection should be administered by your doctor, nurse, or healthcare provider. The detailed instructions on the injection procedure provided at the end of this leaflet should be followed. You should continue to receive SAYANA for as long as instructed by your doctor.

First injection
A dose of 104 mg of SAYANA is given subcutaneously (just under the skin), into the front upper thigh or abdomen every 3 months (12 to 13 weeks). SAYANA will only be effective if you receive your injection at the proper time. To ensure that you are not pregnant at the time of the first injection, it is essential that your first injection be given **ONLY** during the first 5 days of your normal menstrual cycle. After childbirth; If you use SAYANA after having a baby and you are not breastfeeding, the first injection MUST be given within 5 days.
There is evidence that women prescribed SAYANA immediately after childbirth or termination of pregnancy can experience prolonged and heavy bleeding. Because of this, SAYANA should be used with caution at this time.

Further injections
Further doses of SAYANA will then be given every 12 to 13 weeks, (but no later than 14 weeks past your last injection), regardless of when and how much menstrual bleeding you have.
It is important that you receive your next injections at the right time.

If you miss an injection of SAYANA
If you miss your injection or wait longer than 14 weeks between injections, there is a greater risk that you could become pregnant. Tell your doctor, pharmacist, or healthcare professional to find out when you should receive your next injection of SAYANA and which type of contraception should be used in the meantime.

Switching from other Methods of Contraception
When you switch from other contraceptive methods, your doctor will make sure you are not at risk of becoming pregnant by giving you your first injection at the appropriate time. If you switch from oral contraceptives, you should have your first injection of SAYANA within 7 days after taking your last pill.

What if you decide you want to get pregnant
Your usual level of fertility will return when the effect of the last injection has worn off. The time this takes varies in different women, and does not depend on how long you have been using SAYANA. In most women the effect will have worn off 5 to 6 months after the last injection. Over 80 % of women will get pregnant within a year of stopping SAYANA. It is possible to get pregnant in the first month after missing an injection.

4. Possible side effects

Like all medicines, SAYANA can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
There is a small risk of a severe allergic reaction to SAYANA. Serious allergic reactions require emergency medical treatment.

Other side effects include:
Very common side effects (occur in more than 10 out of every 100 patients)
- Weight decrease
- Weight increase

Common side effects (occur in less than 1 out of every 10 patients)
- Abdominal pain (cramps)
- Amenorrhea (very light or no period)
- Depression
- Headache
- Irregular periods
- Decreased sexual feeling
- Heavy, frequent and/or unexpected bleeding
- Acne
- Breast pain / tenderness
- Weakness or tiredness
- Pain at injection site
- Irritability
- Mood changes

Uncommon side effects (occur in less than 1 in 100 patients)
These include:

- Dizziness
- Nausea
- Fluid retention
- Vaginal discharge
- Pain during sexual intercourse
- Pelvic pain
- Change in breast size
- Back pain
- Pain in limbs
- Lack of sleep
- Hot flushes
- Varicose veins
- Hair loss
- Abnormal cervical smear
- Period pains
- Facial discoloration
- Blood clot in the lung
- Hirsutism (abnormal hairiness)
- Feeling bloated
- Vaginal irritation or itching
- Vaginal dryness
- Ovarian cyst
- Premenstrual syndrome
- Change in appetite
- Muscle cramps
- Anxiety
- Migraine
- High blood pressure
- Rash
- Skin irritation
- Abnormal liver function
- Bruising
- Blood clot in the leg

Side effects where frequency is not known

- Joint Pain
- Osteoporosis (weak bones) including oesteoporotic fractures
- Seizures
- Sleepiness
- Abnormal periods (irregular, increase, decrease)
- Galactorrhea
- Blockage of a blood vessel by a blood clot, such as deep vein thrombosis (a blood clot in the leg) or pulmonary embolism (clots in the lungs)
- Rapid heart rate
- Severe allergic reactions (e.g. anaphylaxis, giant hives)
- Yellowing of the skin or eyes (jaundice)
- Itching
- Hives
- Skin stretch marks
- Weakness
- Fever
- Decreased glucose tolerance (excess sugar levels in the blood)
- Increased liver function tests (blood tests to measure the function of the liver)
- Loss of bone mineral density (a test used to diagnose osteoporosis or weak bones)
- Nervousness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse, or healthcare professional

Possible effect on your periods

Most women using SAYANA will experience a change in their bleeding patterns. It is likely that fewer women will experience irregular bleeding, and after 12 months of use 60% will experience little or no bleeding at all.

Possible effect on your bones
SAYANA works by lowering levels of estrogen and other hormones. However, low estrogen levels can cause bones to become thinner (by reducing bone mineral density). Women who use SAYANA tend to have lower bone mineral density than women of the same age who have never used it. The effects of SAYANA are greatest in the first 2-3 years of use. Following this, bone mineral density tends to stabilise and there appears to be some recovery when SAYANA is stopped. It is not yet possible to say whether SAYANA increases the risk of osteoporosis (weak bones) and fractures in later life.

The following are risk factors in the development of osteoporosis in later life. You should discuss with your doctor before starting treatment if you have any of the following, as an alternative contraceptive may be more suitable to your needs;

- Chronic alcohol and/or tobaccoo use
- Chronic use of drugs that can reduce bone mass, e.g. epilepsy medication or steroids.
- Low body mass index or eating disorder, e.g. anorexia nervosa or bulimia.
- Previous low trauma fracture thatr was not caused by a fall.
- Strong family history of osteoporosis.

Teenagers (up to 18 years) Normally, the bones of teenagers are rapidly growing and increasing in strength. The stronger the bones are when adulthood is reached, the greater the protection against osteoporosis in later life. Since SAYANA may cause teenage bones to become thinner at a time when they should be growing, its effect may be particularly important in this age group. Bones start to recover when SAYANA is stopped, but it is not yet known whether the bone mineral density reaches the same levels as it would have if SAYANA had never been used.

You should therefore discuss whether another form of contraception might be more suitable for you with the person who provides your contraception before starting SAYANA.

If you use SAYANA, it may help your bones if you take regular weight-bearing exercise and have a healthy diet, including an adequate intake of calcium (e.g. in dairy products) and vitamin D (e.g. in oily fish).

Possible risk of cancer
Studies of women who have used a range of medicine based contraception found that women who used injectable progestogen like SAYANA for contraception had no increased overall risk of developing cancer of the ovary, womb, cervix, or liver.

Breast cancer is rare under 40 years of age, but the risk increases as a woman becomes older.

There seems to be a slightly increased risk of breast cancer in women who take injectable contraceptives compared to women of the same age who do not use hormonal contraceptives.
This small extra risk of developing breast cancer has to be weighed against the known benefits of medicines like SAYANA. It is not certain whether the injection causes the increased risk of breast cancer. It may be that women receiving the injection are examined more often, so that breast cancer is noticed earlier. The breast

cancer seems less likely to have spread when found in women who receive medicines like SAYANA than in women who do not.

The risk of finding breast cancer is not affected by how long a woman is on the injection, but by the age at which she stops. This is because the risk of breast cancer strongly increases as a woman becomes older. Ten years after stopping hormonal contraceptive injections, the risk of finding breast cancer is the same as for women who have never used hormonal contraceptives.

In 10, 000 women who receive injections like SAYANA for up to 5 years, but stop taking it by the time they are aged 20, it is estimated that less than 1 additional case of breast cancer would be found up to 10 years afterwards, compared with the number found in 10,000 women who had never had the injection.

For 10, 000 women who are on injections like SAYANA for 5 years and stop it by the age of 30, there would be 2 or 3 extra cases of breast cancer found up to 10 years afterwards (in addition to the 44 cases of breast cancer found in 10,000 women in this age group who had never had the injection).

For 10, 000 women who take SAYANA for 5 years and stop it by the age of 40, there would be about 10 extra cases found up to 10 years afterwards (in addition to 160 cases of breast cancer found in 10,000 women in this age group who had never had the injection).

Other risks:
If you develop

- A sudden partial or complete loss of vision, double vision, blood clotting disorders such as pulmonary embolus (blood clot in the lung) or a stroke you should not receive further injections of SAYANA
- Migraine you should consult your doctor before receiving further injections of SAYANA.

5. How to store SAYANA

- Keep out of reach and sight of children.
- Do not refrigerate or freeze.
- Do not use SAYANA after the expiry dates stated on the pre-filled syringe and the carton. The expiry date refers to the last day of that month.

Carefully dispose of any SAYANA suspension that has not been injected. The syringe and needle should NEVER be reused. Any unused product should be disposed of safely after use, in accordance with local guidance for the disposal of sharps.

6. Further information

What SAYANA contains

The active substance is medroxyprogesterone acetate (MPA).
The pre-filled syringe of SAYANA contains 104mg medroxyprogesterone acetate (MPA).

The other ingredients are macrogol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, 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.

What SAYANA looks like and contents of the pack

SAYANA is a white to off-white suspension for subcutaneous injection (an injection given under the skin). It is packed in a pre-filled syringe with a rubber tip cap. A 26G 3/8" needle is also provided.

Marketing Authorisation Holder

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ

Manufacturer

Pfizer Manufacturing Belgium NV/SA
Rijksweg 12
B-2870 Puurs
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom

Pfizer Limited
Ramsgate Road
Sandwich, CT13 9NJ - UK
Tel: + 44 (0) 1304 616161

This leaflet was last approved in {MM/YYYY}**.**

SAYANA®

104 mg/0.65 mL suspension for injection

MEDROXYPROGESTERONE ACETATE

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

SAYANA 104mg/0.65mL suspension for injection
medroxyprogesterone acetate

INSTRUCTIONS FOR ADMINISTRATION: PREPARING AND GIVING A SUBCUTANEOUS INJECTION OF SAYANA

Introduction

SAYANA should be administered by a person (such as your doctor, nurse or healthcare professional) trained in administering subcutaneous injections.

The following instructions explain how to prepare and inject SAYANA. The instructions should be read carefully and followed step-by-step.

The injection should not be mixed with any other medicine.

Instructions for Administration of SAYANA for Subcutaneous Use

Getting ready

Ensure that the medication is at room temperature. Make sure the following components (Diagrams 1 and 2) are available.

Diagram 1

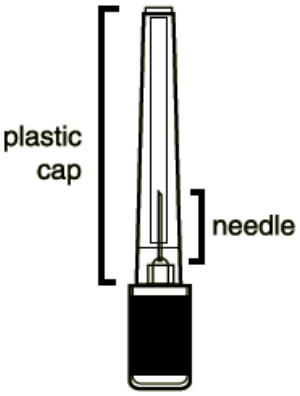
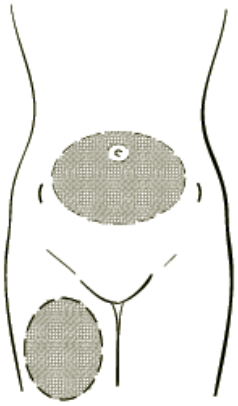


Diagram 2

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

Step 1: Choosing and preparing the injection area.
Choose the injection area. Avoid bony areas and the umbilicus. See shaded areas (Diagram 3).



Upper thigh & Abdomen
Diagram 3

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

Step 2: Syringe preparation
Gently twist off the protective end cap from the needle to break the seal (Diagram 4). Set aside.

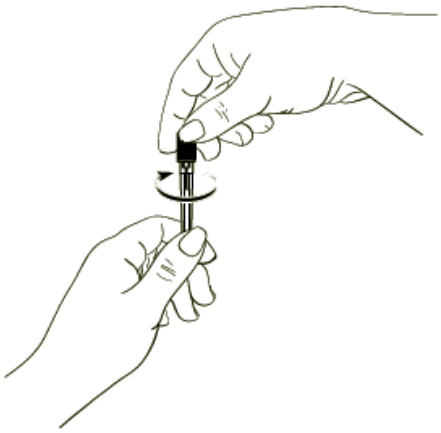


Diagram 4

While holding the syringe firmly by the barrel pointing upward, shake it forcefully for at least 1 minute to thoroughly mix the medication (Diagram 5).

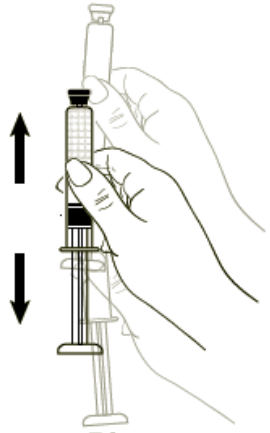


Diagram 5

Hold the syringe barrel firmly, remove the protective tip cap from the syringe and attach the needle by pushing it onto the barrel tip (Diagram 6).

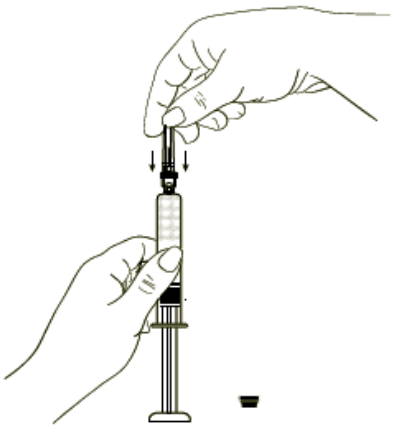


Diagram 6

While continuing to hold the syringe barrel firmly, remove the clear protective plastic cover from the needle, making sure the needle is still firmly attached to the syringe (Diagram 7).

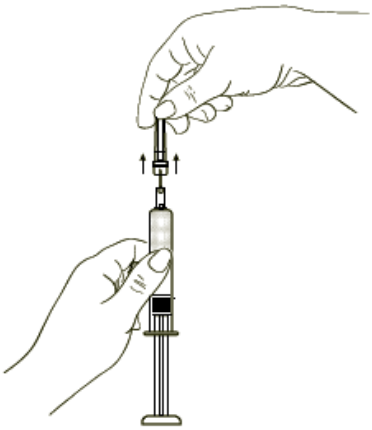


Diagram 7

While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe (Diagram 8).

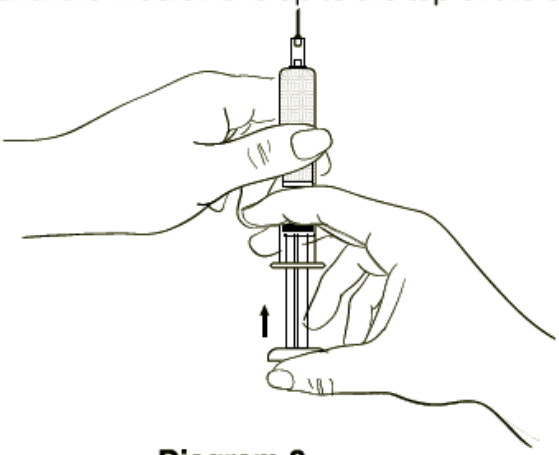


Diagram 8

Step 3: Injecting the dose.

Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and fore-finger (Diagram 9) pulling it away from the body.

Diagram 9

Insert the needle at a 45 degree angle so that most of the needle is in the fatty tissue. The plastic hub of the needle should be nearly or almost touching the skin (Diagram 10).

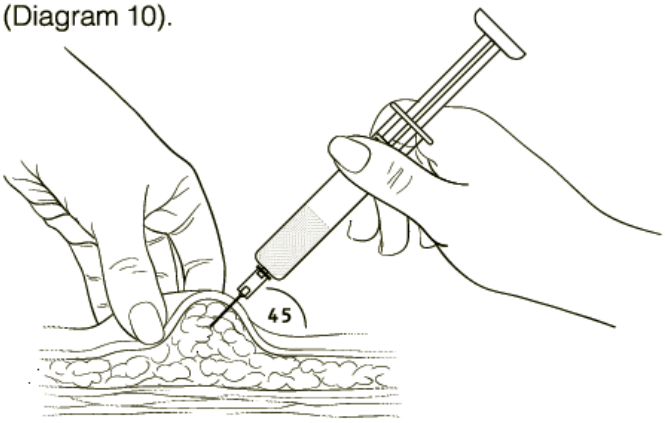


Diagram 10

Inject the medication slowly until the syringe is empty (Diagram 11). This should take about 5-7 seconds.

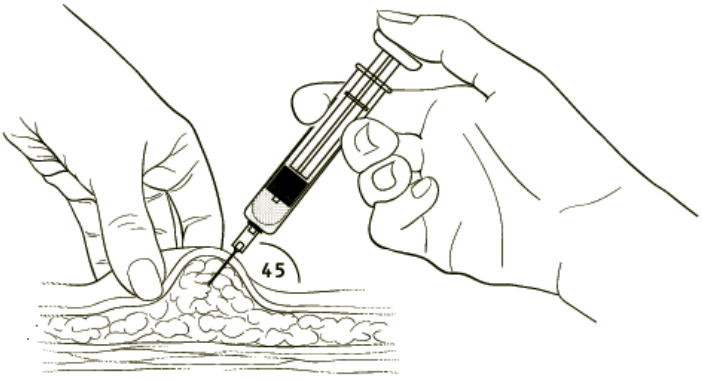


Diagram 11

When the entire dose is completely injected, gently pull the needle out of the skin.

Use a clean cotton pad to press lightly on the injection area for a few seconds. **Do NOT rub the area.**

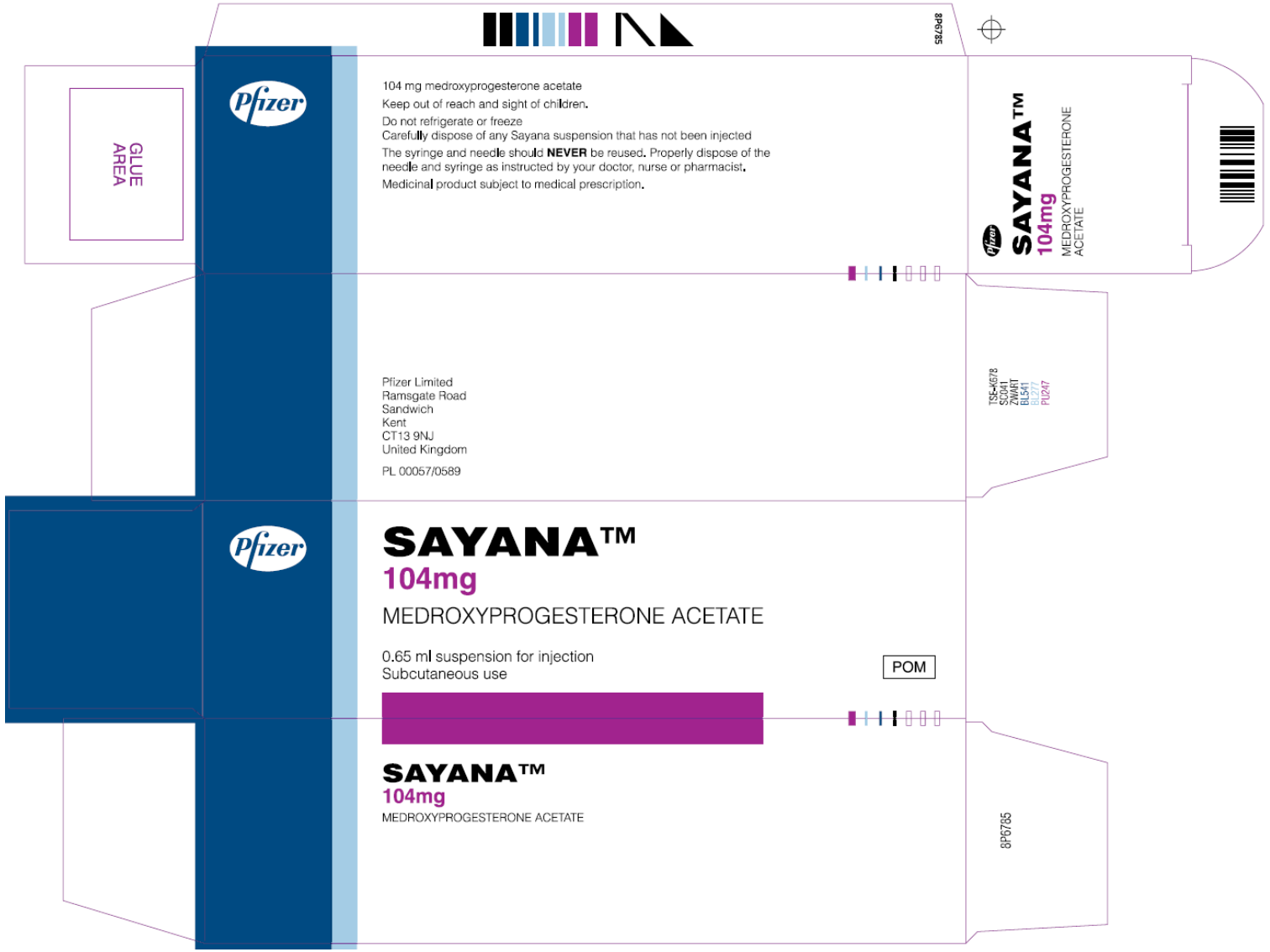
Following the administration of each dose, the used syringe should be discarded in a safe and proper manner.

DISPOSING OF SUPPLIES

The syringe and needle should **NEVER** be reused.

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

Module 4
Labelling



Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 9th July 2007, Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway and Poland granted marketing authorisations to Pfizer Limited for the medicinal product Sayana 104mg/0.65ml Suspension for Injection (UK/H/0960/001/MR). This application was made by Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). A national licence had previously been granted in the UK on 26th October 2005 (PL 00057/0589).

This application was made under Article 8.3 of 2001/83 EC for Sayana 104mg/0.65ml Suspension for Injection, which contains the known active substance medroxyprogesterone acetate.

The contraceptive action of medroxyprogesterone acetate is primarily through inhibition of gonadotrophin secretion, which prevents ovarian follicular maturation and ovulation.

Sayana 104mg/0.65ml Suspension for Injection is indicated for female contraception. It can be used as a long-term contraceptive agent for women of child-bearing potential, but a risk/benefit assessment that takes into consideration the decrease in bone mineral density that occurs during pregnancy and lactation should be performed beforehand, as bone mineral density decreases with long-term Sayana use. In adolescents (12-18 years), it may be used only after other methods of contraception have been discussed and considered unsuitable or unacceptable.

The objective of the development programme was to develop a subcutaneous formulation of depot medroxyprogesterone acetate for contraception that was at least therapeutically equivalent and as tolerable as Depo-Provera intramuscular injections (Pharmacia Limited).

The majority of the non-clinical data have been taken from studies conducted for previous formulations before the introduction of the GLP regulations, and from the literature. However, the studies are considered acceptable. A 13-week local tolerance study on the new formulation was compliant with the GLP regulations.

Clinical studies on Sayana were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Sayana provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sayana 104mg/0.65ml suspension for injection
Name(s) of the active substance(s) (USAN)	Medroxyprogesterone acetate
Pharmacotherapeutic classification (ATC code)	Medroxyprogesterone acetate (G03 AC06)
Pharmaceutical form and strength(s)	Suspension for injection 104mg/0.65ml
Reference numbers for the Mutual Recognition Procedure	UK/H/0960/001/MR
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, The Netherlands, Norway and Poland
Marketing Authorisation Number(s)	PL 00057/0589
Name and address of the authorisation holder	Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, Kent, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

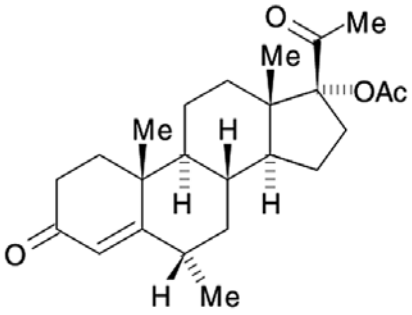
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Medroxyprogesterone acetate

Chemical Name: Medroxyprogesterone Acetate – 17-alpha-acetoxy-6-alpha-methylprogesterone

Structure:



Molecular formula: $C_{24}H_{34}O_4$

Molecular weight: 386.5

Physical form: A white to almost white, crystalline powder, practically insoluble in water, freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and in methanol and slightly soluble in ether.

CAS registry: 71-58-9

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance medroxyprogesterone acetate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and Certificates of Analysis have been provided for any working standards used.

Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. The data support a retest period of 2 years, when stored at ambient room temperature/humidity. The applicant has provided suitable commitments to present further results from these and any new studies as they become available.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients macrogol, methyl parahydrobenzoate, propyl parahydrobenzoate, sodium chloride, polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, hydrochloric acid, sodium hydroxide and water for injection. With the exception of monobasic sodium phosphate (which is controlled to a US Pharmacopoeia monograph), all excipients are controlled to their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for these applications.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished product is supplied in a disposable glass syringe, with a bromobutyl rubber plunger and tip cap. A 26G, 3/8” needle is provided separately.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and comply with guidelines concerning materials in contact with parenteral products.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 36 months has been set, with the following storage conditions: “Do not refrigerate or freeze”.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

PHARMACODYNAMICS

The pharmacodynamics of medroxyprogesterone acetate are well-established and will not be reproduced in detail here. Briefly, studies in animals have demonstrated effects of medroxyprogesterone acetate on suppression of ovulation, interference with fertilisation and/or the normal development of the ovum. The contraceptive action of medroxyprogesterone acetate is primarily through inhibition of gonadotrophin secretion, which prevents ovarian follicular maturation and ovulation, and causes endometrial thinning. Medroxyprogesterone acetate is thought to moderate endometeriosis via suppression of ovarian function and possibly by decreasing peritoneal inflammation.

Secondary Pharmacodynamics
Secondary effects of medroxyprogesterone acetate are related to interactions with other steroid hormone receptors including mineralocorticoid receptors, effects on growth hormone and glucose metabolism.

Safety Pharmacology
The applicant has not conducted any safety pharmacology studies. A review of the literature has been provided and it was concluded that there are no concerns in respect of the central nervous, respiratory or cardiovascular systems. No data on other systems or pharmacodynamic drug interactions were found in the literature.

PHARMACOKINETICS

The non-clinical pharmacokinetic information for medroxyprogesterone acetate is derived from studies using intramuscular (IM) administration and from studies on medroxyprogesterone acetate: estradiol cypionate (E2C), a combination injectable contraceptive agent, supplemented with data from the literature. Uptake following subcutaneous dosing is slower than that following intramuscular dosing.

There were no pharmacokinetic interaction studies discussed in the non-clinical overview.

Absorption, Distribution, Metabolism and Excretion (ADME)
In dogs and monkeys, medroxyprogesterone acetate entered the circulation more slowly from intramuscular dosing than from oral, by factors of six and ten respectively. It has also been shown that absorption in humans from the muscle is slower than from the gastrointestinal tract.

In rats, the percentage of free drug following intravenous or oral dosing was five, with the remainder mostly bound to albumin. There was no specific localisation of medroxyprogesterone acetate. In humans, it has been found to cross the placenta.

In dogs, monkeys, rats and humans, no unchanged medroxyprogesterone acetate was present in the urine after oral administration or in monkeys and human following IM administration.

Identified metabolites of medroxyprogesterone acetate include the 17-acetate of 6α-methyl-6β,17α,21-trihydroxy-progesterone, and medroxyprogesterone. In humans by the oral and IM routes, approximately twenty-five percent of the urinary metabolites were unconjugated and non–polar. Approximately half of the remaining material was conjugated, primarily as glucuronides and was made non-polar by enzymatic hydrolysis. In dogs, medroxyprogesterone acetate was found not to induce either α1-acid glycoprotein or hepatic cytochrome P_{450}, but in rats and humans, it is known to induce the latter.

Excretion in dogs and monkeys following oral or IM administration was slower in the case of the latter by factors of five and ten respectively. In humans, intravenously administered medroxyprogesterone acetate is secreted directly into the bile and this route is also predominant following IM and oral dosing. To a lesser extent, medroxyprogesterone acetate is excreted in the urine as conjugates and polar metabolites.

TOXICITY

The non-clinical overview concentrates on toxicity studies conducted by the SC or IM routes. Data on other routes are presented in the tabulated summaries and additional data from the literature in the narrative summaries.

Single-dose toxicity

The acute median lethal doses (LDs_{50}) by the SC route in mice and rats were greater than 4000 mg/kg and greater than 8000 mg/kg respectively. Single doses of between 3 and 4.8mg/kg in beagle and foxhound dogs were associated with a decrease in prostate size but there were no effects on the haematogram, testes or semen quality.

Repeat-dose toxicity

Medroxyprogesterone acetate was considered not to result in untoward toxicity at doses up to fifteen times the therapeutic dose in humans in repeat-dose studies in mice, rats, rabbits, dogs and monkeys, but effects consistent with long-term administration of progestogens were noted. Changes included increased body weight and endocrine-related organ effects.

Genetic toxicity

In vitro and *in vivo* studies conducted by the applicant and a review of the literature did not reveal any evidence of genotoxicity on the part of medroxyprogesterone acetate.

Carcinogenicity

Life-time studies in mice, rats, dogs and monkeys have been conducted by the IM route. Because the dog is extremely sensitive to the effects of progestogens, it is considered unsuitable for testing for their carcinogenicity, and the data from the dog studies have not been included in the safety assessment. Mammary tumours in mice were seen with high doses of medroxyprogesterone acetate; however a study conducted in women by the World Health Authority did not reveal an increased risk of breast cancer. Findings of endometrial carcinomas and papilliferous fibroadenomas of the cervix in monkeys were considered not relevant to the human and medroxyprogesterone acetate was deemed not to be carcinogenic.

Reproductive and developmental toxicity

Medroxyprogesterone acetate has been shown to have adverse effects on reproduction in animals, but it is not intended for use during pregnancy and appropriate warnings are included in the Summary of Product Characteristics (SPC).

IM injection in rabbits at doses up to 10 mg/kg in females and 30 mg/kg in males resulted in reversible effects on fertility.

The applicant has not conducted any studies investigating embryo-fetal development or juvenile toxicity with the new formulation.

Local tolerance
A single subcutaneous dose in female rabbits with thirteen weeks of follow-up revealed some localised inflammatory changes but, in general, the treatment was well-tolerated.

Excipients
Given that the application is for lower doses of a well-established therapy, there is no need to re-evaluate the preclinical data here. The non-clinical overview contains a concise account of the data relevant to the clinical indication. The absence of new studies by the clinical route is justified because the absorption by the SC route is slower than that with IM administration, and the dose is lower than that of existing IM products. The local tolerance of the new SC product was demonstrated satisfactorily to supplement the data from IM dosing and from the literature.

ENVIRONMENTAL RISK ASSESSMENT (ERA)
The Predicted Environmental Concentration (PEC) of medroxyprogesterone acetate is below the threshold of concern stipulated in the CPMP guidance and no further assessment is required.

The PEC was calculated by a suitably qualified company employee.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory from a non-clinical viewpoint.

NON-CLINICAL OVERVIEW
The non-clinical overview was written by a suitably qualified person.

CONCLUSION
There is no objection to the grant of a licence from a preclinical point of view.

III.3 CLINICAL ASPECTS

Pharmacokinetics
The Marketing Authorisation Holder initiated a clinical programme to develop a subcutaneous (SC) formulation of depot medroxyprogesterone acetate for contraception. Development was based on the results of a dose-finding study, which indicated that 104mg (in 0.65mL) injected three-monthly would reliably suppress ovulation over the dosing interval. Sayana 104mg/0.65ml Suspension for Injection is, therefore, expected to be therapeutically equivalent in efficacy to the currently marketed Depo-Provera intramuscular injections (Pharmacia Limited), if not better as it contains a lower dose of the active ingredient (104mg vs 150mg). It is also anticipated, by the Marketing Authorisation Holder, that women may have better compliance with Sayana 104mg/0.65ml Suspension for Injection due to ease of injection.

Pharmacodynamics
This application is for Sayana 104mg/0.65ml Suspension for Injection, containing 104mg/0.65ml of the active substance, medroxyprogesterone acetate. Medroxyprogesterone acetate is a synthetic analogue of 17α-hydroxyprogesterone, which has anti-oestrogenic, anti-androgenic and anti-gonadotrophic properties. Medroxyprogesterone acetate exhibits well-known pharmacological effects on reproduction-related functions and has a wide therapeutic index.

Clinical efficacy
The design and conduct of the pivotal contraceptive efficacy trials are considered adequate to support this application. Data showed that Sayana 104mg/0.65ml Suspension for Injection was an effective contraceptive in the relevant target population, which included a substantial number of the most fertile subgroup (aged ≤ 35 years) who completed a year of treatment. There were no pregnancies due to treatment failure in Phase III, which included 17,528 woman cycles (excluding months when intercourse did not take place or a barrier method was used). The upper limit of a 95% confidence interval for the Pearl Index is 0.27 (Statistical Assessor's calculation) and as this is much less than 1 these clinical studies provide sufficient evidence of contraceptive efficacy.

Clinical safety
An important part of the rationale for developing Sayana 104mg/0.65ml Suspension for Injection is the expectation that it would have a safety profile at least comparable to Depo-Provera intramuscular injections (Pharmacia Limited). The overall safety profile of Sayana 104mg/0.65ml Suspension for Injection from the Phase III studies is consistent with that of the marketed Depo-Provera intramuscular injections and reflects the known physiological effects of medroxyprogesterone acetate. The most frequently reported adverse events associated with Sayana 104mg/0.65ml Suspension for Injection were comparable to the most frequent events seen with intramuscular injections and cited in the existing product literature for Depo-Provera, with the exception of injection site reactions. These appear to be more frequent for the subcutaenous Sayana formulation, a finding consistent with other subcutaenous products in general, and this is not felt to constitute a significant safety concern.

The only new safety concern arising is the apparent reversal in bone mineral density accretion in adolescent girls receiving the intramuscular formulation. These study findings have resulted in a variation of the Depo-Provera SPC and the Sayana SPC has been amended in line with this.

Clinical Conclusion
A Marketing Authorisation may be granted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Sayana 104mg/0.65ml Suspension for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Sayana 104mg/0.65ml Suspension for Injection beyond those already described.

EFFICACY

The finished product has been shown to be efficacious in the target population. With the exception of injection site reactions (which do not constitute a significant safety concern, the level of adverse events were considered comparable to the already marketed product Depo-Provera intramuscular injections (Pharmacia Limited).

One new safety concern (reversal in bone mineral density accretion in adolescent girls receiving the intramuscular formulation) has resulted in the amending of the SPCs for both products to account for this.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical concerns have been identified. The one new clinical concern raised has been accounted for in a revision of the SPCs for both products. Extensive clinical experience with medroxyprogesterone acetate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
11/09/2007	Type II Variation	To update the clinical information (SPC) for the national license following completion of the MRP (UK/H/960/01/MR).	Approved
11/09/2007	Type II Variation	To update the quality section of the dossier following completion of MRP - UK/H/960/01/MR as per the changes recommended during the MRP.	Approved
19/05/2008	Type II Variation	To change the secondary packaging of the product by removing the alcohol swab from the finished product package-consequentially leaflet (healthcare professionals section) is updated.	Approved
22/04/2009	Type II Variation	To update section 5.1 (Pharmacodynamic properties) of the SPC following the revision of the Core Data Sheet to include new study results investigating bone mineral density predominately in adolescent females.	Approved
21/04/2009	Type II Variation	To update section 4.4 (Special warnings and precautions for use) of the SPC by including a new study results investigating bone mineral density and fracture rates.	Approved
07/04/2009	Type II Variation	To update section 4.8 (Undesirable effects) of the SPC and consequentially the leaflet with the term ‘skin striae’.	Approved
21/04/2009	Type II Variation	To update sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.6 (Pregnancy and lactation) and 4.8 (Undesirable effects) of the SPC and consequentially the leaflet following revision of the Core Data Sheet and to align with the Depo-Provera IM SPC.	Approved