Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Medroxyprogesterone acetate

Proprietary Product Name: Sayana

Sponsor: Pfizer Australia Pty Ltd

July 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (New Route of Administration)
Decision:	Approved
Date of Decision:	23 June 2011
Active ingredient(s):	Medroxyprogesterone acetate (MPA)
Product Name(s):	Sayana
Sponsor's Name and Address:	Pfizer Australia Pty Ltd 38-42 Wharf Rd, West Ryde, NSW 2114.
Dose form(s):	Suspension for Injection
Strength(s):	104 mg/ 0.65 mL (160 mg/mL nominally)
Container(s):	Pre-filled syringe with listed needle in a Procedure pack.
Pack size(s):	One per pack
Approved Therapeutic use:	***Endometriosis:*** *For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra-indicated or has been unsuccessful.* ***Contraception (ovulation suppression):*** *For long-term prevention of pregnancy in women when administered at 3-month intervals.* *Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use SAYANA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see PRECAUTIONS)."*
Route(s) of administration:	Subcutaneous (SC)
Dosage:	All 104 mg is to be given. Dose interval is 12-14 weekly with no adjustment for body weight.
ARTG Number (s)	167889

Product Background

This AusPAR describes the evaluation of an application by Pfizer Australia Pty Ltd (the sponsor) to register Sayana, representing a new dosage and route of administration (SC) for medroxyprogesterone acetate (MPA). The active ingredient has had a very long and notable regulatory history. The Australian regulatory history goes back to the late 1960s.

The proposed dose of MPA is lower for Sayana compared to the currently registered Depo-Provera formulation (104 mg SC compared to 150 mg intramuscularly (IM), administered once every 3 months) and resultant exposure is also less. The strength of the active ingredient MPA is however higher with the new product (160 mg/mL compared to ≤150 mg/mL) and the excipient profile is altered. The new proposed formulation varies by inclusion of additional excipients and includes phosphate buffers.

The IM formulation is currently approved for contraceptive use in many countries. It is also indicated in the treatment of metastatic breast cancer, endometrial and renal cell carcinoma. An oral formulation is available for the treatment of secondary amenorrhoea and abnormal uterine bleeding due to hormonal imbalance. In Australia, the relevant registered indications for the IM Depot-Ralovera 50 mg/mL and 150 mg/mL and Depot-Provera 50 mg/mL and 150 mg/mL are:

- Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-points of treatment is pregnancy or for the control of symptoms when surgery is contra-indicated or has been unsuccessful.
- Contraception (ovulation-suppression): For the long-term prevention of pregnancy in women when administered at 3-month intervals. Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use Depot-Ralovera long term (greater than two years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see *Warnings*).

Sayana is also proposed to be used for long term contraception and for the treatment of endometriosis.

In recent decades, the major interest concerning depot MPA has centred upon bone mineral density (BMD) loss, identified by a group of New Zealand researchers as well as a Women's Health Initiative (WHI) study[1] implicating orally administered MPA as an unequivocal promoter of breast cancer when used with conjugated equine oestrogens.

Regulatory Status

Sayana is registered in numerous overseas countries including the USA. The marketing authorization status for Sayana suspension for SC injection in the major markets is identified in Table 1.

Table 1. Overseas regulatory status

Market	Status	Act Approval Date	Indication
Canada	Approved	29 July 2010	Contraception
Germany	Launched	30 November 2007	Pregnancy, prevention, long-term (3 months), in women who do not tolerate other methods of contraception.
United Kingdom	Approved	26 October 2005	Pregnancy, prevention, long-term (3 months), in women who do not tolerate other methods of contraception.
USA	Launched	17 December 2004	Pain, associated with endometriosis management, Pregnancy, prevention

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

[1] Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women Principal Results From the Women's Health Initiative Randomized Controlled Trial. Writing Group for the Women's Health Initiative Investigators. *JAMA* 2002; 288:321. http://jama.ama-assn.org/content/288/3/321.full

II. Quality Findings

Introduction

The proposed Sayana product is to be indicated for the same endometriosis and contraception (ovulation suppression) indications (only). Thus, unless there are clinical data to independently support these indications, bioequivalence of the two formulations and routes of administration will be important.

There are British Pharmacopiea (BP) and United States Pharmacopeia (USP) monographs for drug substance and finished injection suspension containing this drug substance.

Drug Substance and Drug Product

Chemistry and Quality Control

All details relating to the medroxyprogesterone acetate drug substance are as for the previously registered products. The drug substance is sterilised (ethylene oxide) at a separate site of manufacture and this site has Good Manufacturing Practice (GMP) Clearance.

Compared to the 150 mg/1 mL Depo-Provera, the proposed product contains similar quantities of the same excipients but it also contains the additional excipients sodium phosphate monobasic and sodium phosphate dibasic dodecahydrate (as a buffer), methionine and povidone. The hydroxybenzoates are present as resuspending agents The specifications of the product have acceptable expiry limits and release limits that allow for the changes that occur over the shelf life.

Stability data was provided that supported an unopened shelf life of 3 years when stored below 25ºC with the additional storage condition of 'do not freeze'.

Secondary Evaluations

The following secondary evaluations were performed and found to be acceptable:

- Endotoxins
- Container Safety
- Sterility/microbiology (in relation to both manufacture and the finished product)
- Transmissible spongiform encephalography (*materials used in the synthesis of the drug substance were of animal origin*).

Biopharmaceutics

The sponsor stated that the proposed product was used in the Phase III efficacy studies. This would suggest that the current Australian submission included clinical data to independently support the proposed indications. However the issue of bioequivalence of the two formulations and routes of administration was raised.

Studies Evaluated

The submission included one bioavailability study to compare the bioavailability from two different sites of administration.

Study 839-FEH-0012-271 was a parallel group study to compare the subcutaneous (SC) bioavailability from two sites of administration: anterior thigh and abdomen[2]. The results indicated higher bioavailability (maximal plasma concentration (Cmax), $C_{\_91}$[3] and area under the plasma concentration time curve (AUC_{0N})[4]) from the thigh compared to the abdomen. *Note AUC_{0N} is considered a better indicator of bioequivalence than $AUC_{0-\infty}$.* The concentration time profile is shown in Figure 1 and the pharmacokinetic (PK) paramaters for the abdomen injection site and the leg injection site are shown in Tables 2 and 3 respectively.

Figure 1. MPA concentration Time Profile after a single DMPA-SC dose of 104 mg/0.65 mL in Asian Women by Injection site (n=12).

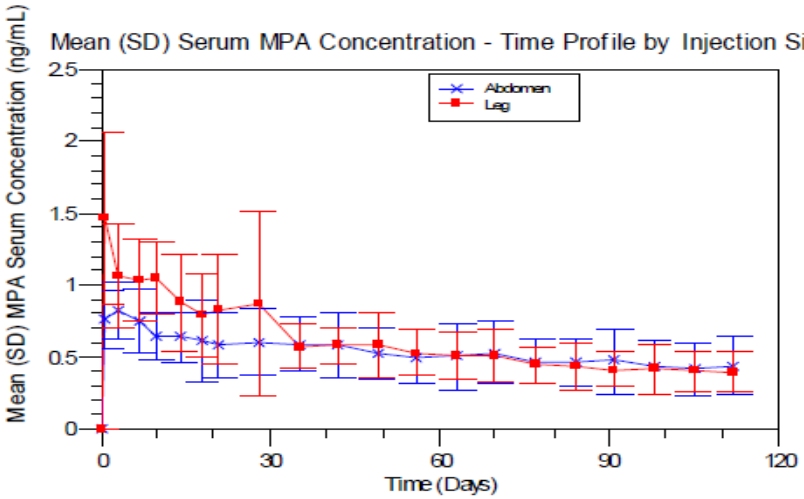


Table 2. Pharmacokinetic (PK) parameter summary statistics for Injection site=Abdomen.

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
AUC0_91	12	60.032	16.3399	65.9336	24.4015	78.308
AUC0N	12	60.155	16.3480	66.0123	24.4789	78.390
AUCTOT	12	123.748	84.4139	84.0200	30.6340	330.239
CMAX	12	0.943	0.2059	0.9200	0.5930	1.410
TMAX	12	21.917	29.8830	8.5000	1.0000	91.000
LZ	11	0.010	0.0057	0.0079	0.0027	0.020
THALF	11	103.748	71.5215	87.2551	33.9516	260.938
C_91	12	0.470	0.2214	0.3795	0.1460	0.890

[2] Given the long sampling period, the parallel design is acceptable.
[3] $C_{\_91}$ = concentration at Day 91 after dosing.
[4] AUC_{0N} = AUC from time 0 to 112 days.

Table 3. Pharmacokinetic (PK) parameter summary statistics for Injection site=Leg.

PARM	N	MEAN	STD	MEDIAN	MIN	MAX
AUC0_91	12	67.754	15.8817	67.889	41.6298	95.873
AUC0N	12	68.171	16.1678	68.060	41.7675	96.265
AUCTOT	12	112.522	47.2960	101.441	62.2811	242.738
CMAX	12	1.652	0.6649	1.775	0.6820	2.840
TMAX	12	4.333	7.8894	1.000	1.0000	28.000
LZ	12	0.011	0.0074	0.011	0.0041	0.033
THALF	12	80.971	44.2389	65.965	21.2705	170.279
C_91	12	0.412	0.1231	0.426	0.2330	0.651

The sponsor claimed that the injection site did not impact the overall concentration time course, but 90% confidence intervals were not calculated and given the differences in mean results and the variation in the results, these are likely to be outside of 0.80-1.25. The quality evaluator suggested that the Delegate should consider whether bioequivalence was necessary and what clinical data was provided to support the use of both injection sites.

Justification for Not Providing Bioavailability Data

No data were provided comparing SC administration to IM administration. The sponsor argued that bioequivalence of "Sayana" and "Depo-Provera" (used with IM administration) is not intended, anticipated or necessary. The Delegate should note that this justification does not address the usual points from Appendix 15 of the ARGPM[5] but that bioequivalence is not claimed. Further the biopharmacodynamic equivalence was studied in Study 839-FEH-0012-272 (see Clinical Findings below). It was therefore suggested that in relation to whether patients can be switched from Depo-Provera to Sayana, if a statement is required then, the PI should reflect the results from Study 839-FEH-0012-272.

Quality Summary and Conclusions

Given that the proposed product is similar to registered products and biopharmacodynamic equivalence of SC and IMK administration was studied in Study 839-FEH-0012-272, the advice of PSC was not sought.
Approval of this submission was recommended with respect to the chemistry and quality.

In relation to bioavailability:

- The PI states that the product can be administered into the anterior thigh or the abdomen. The responses from these two sites have not been shown to be bioequivalent, but the sponsor argued that this is a not an issue as the C_{min} Day 91 results are similar.

[5] Australian Regulatory Guidelines for Prescription Medicines: Appendix 15: Biopharmaceutic studies. www.tga.gov.au/pdf/pm-argpm-ap15.pdf

- No data have been provided comparing SC administration to intramuscular (IM) administration but the sponsor argued that this was not intended, anticipated or necessary for this submission.

III. Nonclinical Findings

Introduction

Nonclinical data submitted by the sponsor dealt chiefly with general aspects of the pharmacology, pharmacokinetics and toxicology of medroxyprogesterone acetate, and was principally in the form of published papers (mostly dating to the 1980s or earlier). There were three toxicity studies that involved administration of the drug by the newly proposed route (SC) and these data were the focus of the evaluation.

Relative exposure

Human exposure to medroxyprogesterone acetate at the maximum recommended dose of Sayana (104 mg SC) is less than that for Depo-Provera, the existing product for IM injection (150 mg). $AUC_{0-\infty}$[6] is ~12–30% lower and C_{max} is ~60% lower.

Pharmacology

No new data were submitted under this heading.

Pharmacokinetics

No new data were submitted under this heading.

Toxicology

Medroxyprogesterone acetate displayed a low order of acute toxicity by the SC route in previously evaluated studies in rodents (50% lethal dose (LD_{50}) >4000 mg/ kg in mice and >8000 mg/ kg in rats).

Chronic repeat dose toxicity studies in mice (18 months duration) and rats (22 months duration), involving once monthly SC administration of the drug, were submitted in the current application. These studies were non-Good Laboratory Practice (GLP) compliant (conducted in the late 1970s prior to the implementation of GLP regulations) but were adequately documented. Findings in mice treated at 25 mg/ kg were limited to occasional transient post-dose polyuria and organ weight changes (increased bodyweight-relative adrenal weight and decreased combined relative uterus, cervix and ovaries weight); this dose is >3 times the maximum recommended human dose for Sayana when adjusted for body surface area and dosing frequency (monthly doses in the toxicity study compared to administration once every 3 months in clinical use). In rats, treatment with medroxyprogesterone acetate at 25 mg/ kg (estimated relative exposure, ~7) also affected organ weights (decreased bodyweight-relative adrenal and combined uterus, cervix and ovaries weights) and was associated with a range of microscopic lesions (bone marrow atrophy, focal interstitial myocarditis, chronic glomerulonephritis, absent corpora lutea, pituitary hyperplasia and thymic atrophy). No treatment related increase in neoplastic lesions was observed with the drug in either study. The findings are consistent with hormonal effects from long term progestogen administration, non-specific toxicity and/or those of previously evaluated studies in animals by the IM or oral (PO) routes.

[6] AUC from time 0 to infinity.

Although the clinical dose and systemic exposure for medroxyprogesterone acetate is lower with the proposed SC product compared to the existing IM ones, the strength of the active ingredient is marginally higher (160 compared to 150 and 50 mg/mL). Formulation differences also exist in terms of the excipient profile. A local tolerance study was conducted with Sayana in rabbits and indicated that the product was well tolerated following SC injection. The study was GLP compliant and involved administration of the full human dose (0.65 mL). Inadvertent intradermal administration was less well tolerated, producing minimal to slight injection site reactions (erythema/oedema), slight degeneration of adjacent connective tissue and slight focal myositis in the cutaneous muscle.

Nonclinical Summary and Conclusions

- The drug displayed a low order of acute toxicity by the SC route in mice and rats.
- Chronic repeat dose toxicity studies in mice (18 months duration) and rats (22 months), involving once monthly SC administration of medroxyprogesterone acetate, revealed findings consistent with hormonal effects from long term progestogen administration, non-specific toxicity and/or ones seen in previously evaluated studies in animals by other (IM or PO) routes.
- Sayana was well tolerated following SC injection in rabbits.
- There were no nonclinical objections to the registration of Sayana for the proposed indications.

IV. Clinical Findings

Introduction

Depot-medroxyprogesterone acetate (DMPA) is an aqueous suspension of medroxyprogesterone acetate (MPA), a synthetic analog of 17α-hydroxyprogesterone. DMPA has been available for many years as an intramuscular (IM) injection. The formulation for marketing (subcutaneous (SC) formulation (DMPA-SC)) contains 160 mg/mL or 104 mg/0.65 mL per injection. The aim of developing a subcutaneous formulation was to have a more patient-acceptable delivery suitable for self-administration. The clinical program for DMPA-SC comprises eight completed studies, including three Phase I/II clinical pharmacology studies, three Phase III efficacy and safety studies for the contraception indication and two Phase III studies for the endometriosis indication. All studies were sponsored by Pharmacia (Pfizer).

The sponsor stated that the dose is supported by a dose finding study (Study 265 M5V2P18-22) and that a pharmacokinetic-pharmacodynamic study (Study 271) in Asian women and another "comprehensive" pharmacokinetic-pharmacodynamic study (Study 272) were also provided. There is no mention of a formal, comparative steady state pharmacokinetic/bioavailability study. The three Phase I/II studies and three Phase III studies were submitted to support contraception and the two six month comparative (against leuprorelin, referred to in the report as leuprolide) Phase III studies are submitted to support use in endometriosis.

The sponsor stated that there is no paediatric clinical development program and Sayana has not been studied in women under 18 years of age. They state that data are available on DMPA-IM in adolescents.

Risk management plans (RMP) Version 1.0 dated 13 October 2006 and Version 1.1 dated 1 June 2007 for the European Union were provided. It was unclear if this is to cover

Australia as well. Included with the RMP were the protocol and results of a comparative study of the effect of DMPA-IM on the incidence of bone fracture in the United Kingdom (UK) using the General Practice Research Database (GPRD).

Good Clinical Practice (GCP) Aspects

The sponsor certified that all clinical studies were conducted in accordance with GCP guidelines, together with appropriate permission from independent ethics committees or institutional review boards and health authorities.

Clinical Pharmacology

The clinical pharmacology studies included three single dose studies which enrolled 139 women. These were a dose finding study (Study 265), a pharmacokinetic (PK) / pharmacodynamic (PD) study in Asian women (Study 271) and a PK/PD study in which DMPA-SC was compared to DMPA-IM (Study 272). Study design was similar for the three trials, with a control cycle to confirm ovulation, a treatment phase of 13 weeks and a follow up phase from 3 to 39 weeks. The impact of body mass index (BMI), race/ethnicity, and the SC injection sites (anterior thigh vs abdomen) on the PK/PD profiles of MPA were also evaluated.

In the initial dose finding Study 265, the formulations used were the marketed DMPA-IM products (Depo-Provera Sterile Aqueous Suspension 400 mg/mL and Depo-Provera Contraceptive Injection 150 mg/mL), diluted with sterile saline to achieve appropriate dose levels at a constant volume. The subcutaneous formulation (DMPA-SC 104 mg/0.65mL) was then developed and used in all other clinical trials. The sponsor stated that the differences between IM and SC formulations are minor and therefore no bridging study has been conducted.

From Study 265, 100 mg was the chosen dose for further evaluation of suppression of ovulation (as measured by serum progesterone levels) together with serum MPA concentration. As the SC formulation is 16% w/v, 100 mg MPA would require a 0.625 mL injection volume. This volume was rounded to 0.65 mL giving a dose of 104 mg MPA per injection.

Pharmacokinetics

Introduction

Three Phase I/II single dose studies included in the current Australian submission provided PK data. Multiple dose studies were not conducted as the sponsor stated the single dose is predictive of multiple dosing based on information from DMPA-IM. PK data was also collected in the Phase III Study 267BMD.

Methods

As well as assessment of serum MPA levels, quantitation of 17β-estradiol (E_2), progesterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) in human serum was also conducted.

Pharmacokinetic parameters of MPA were determined by non-compartmental methods. The observed peak concentrations (C_{max}) and time to peak concentrations (T_{max}) were reported. Apparent terminal rate constants (λz) were estimated and half-life ($t_{½}$) and the area under the serum concentration-time curve from time zero to the last quantifiable serum concentration ($AUC_{0\text{-}t(last)}$) were calculated. The area was extrapolated to infinity ($AUC_{0\text{-}\infty}$) by adding $C_{t(last)}\ \lambda z$ to $AUC_{0\text{-}t}$, where $C_{t(last)}$ is the last quantitated serum concentrations.

Absorption

Specific biopharmaceutic studies with DMPA-SC were not conducted. From the 3 PK studies it is noted that there is prompt absorption from the subcutaneous injection site as therapeutic levels of MPA are reached within 24 hours. The effect of injection site on absorption is discussed in section below.

Distribution/Elimination/Metabolism

The sponsor stated the distribution and protein binding as well as metabolism and elimination of DMPA-SC would be the same as for the approved DMPA-IM and no new data were submitted in this current Australian submission.

Dose proportionality and time dependency

In Study 265, the PK of four doses of MPA were examined after a single subcutaneous dose in 46 healthy women aged 18 to 45 years. Absorption occurred promptly with MPA concentrations at, or above, 0.20 ng/mL by 24 hours post dose (the first sampling point). The mean serum MPA concentration increased with increasing dose of DMPA-SC, with slow absorption and peak concentrations at 2-3 weeks post dose and sustained levels to Day 91. The mean (standard deviation (SD)) serum MPA concentrations at Day 91 (just before the next scheduled injection) were 0.174 (0.082), 0.253 (0.111), 0.332 (0.137), and 0.495 (0.215) ng/mL in the 50 mg, 75 mg, 100 mg and 150 mg dose groups, respectively. At Day 91, MPA levels were above the 0.20 ng/mL threshold for ovulation suppression[7] in the 100 mg and 150 mg dose groups, though MPA levels had dropped below this threshold level in a number of women in the 50 mg and 75 mg groups. The AUC and trough Day 91 concentration (C91) of MPA increased with increasing dose; although there was overlap and data were suggestive of linearity based on single doses (r=0.685, p=0.0001 and r=0.649, p=0.0001, respectively). The apparent half life was variable, ranging from 27 to 37 days.

In Study 271, the PK of a single dose of 104 mg/0.65 mL were assessed in 24 healthy Asian women aged 18 to 40 years. For the whole group, the mean C_{max} was 1.3 ng/mL (SD 0.6), T_{max} was at 13 days and C_{91} was 0.441 ng/mL (SD 0.187). The half life was variable with a mean of 91 days and SD of 59 days.

In Study 272, there were 42 healthy women aged 18 to 40 years who received a single dose of DMPA-SC and had PK data. As with Study 271, there was quick commencement of absorption with MPA concentrations above 0.2 ng/mL by 24 hours. The mean T_{max} was reached at about 8 days post dose with a mean C_{max} of 1.56 ng/mL (range 0.53 ng/mL to 3.08 ng/mL). At Day 91, 40/42 subjects had concentrations above 0.2 ng/mL (with two women having C_{91} trough levels below the threshold level (0.133 and 0.150 ng/mL). The half life was again variable with a mean of 43 days and a range of 15 to 114 days.

In the Phase III Study 267BMD, MPA trough (C_{min}) levels were collected after 6, 12 and 24 months of treatment in women who had received DMPA-SC (104 mg) and DMPA-IM (150 mg). The mean C_{min} values were 0.66 ng/mL , 0.79 ng/mL and 0.87 ng/mL after 2, 4 and 8 injections of DMPA-SC which were slightly lower than DMPA-IM (0.80 ng/mL , 0.79 ng/mL and 1.03 ng/mL). The median change (from Month 6) in C_{min} was 0.09 ng/mL at Month 12 and 0.16 ng/mL at Month 24. From these results it would appear that there is a minimal increase in serum levels following multiple injections.

[7] The sponsor stated the MPA concentration threshold for ovulation suppression of 0.20 ng/mL is based on data from Pharmacia and Upjohn study of Cyclo-Provera.

Intra- and inter-individual variability

There was a high degree of inter-subject variability in serum MPA levels found in all three studies. In Study 265, the mean C_{max} was 0.89 ng/mL and the mean T_{max} was 21 days on Day 91 for the 100 mg dose. In Studies 271 and 272, the mean C_{max} was 1.30 and 1.56 ng/mL , the mean T_{max} was 13 days and 8 days, mean $t_{½}$ 92 days and 43 days, and mean AUC_{0-91} was 64 (SD 16) and 67 (SD 24) ng/mL, respectively.

In Study 265, one woman had an unusual PK profile with an immediate high level which was followed by a rapid decline to 0.167 ng/mL by Day 49. The study investigators suggested that this was most likely due to injection into, or in close proximity to, a blood vessel.

Injection site

In Study 265, while MPA C_{91} levels appeared similar between injection sites (abdomen and thigh) but there were no statistical assessments of the difference. In Study 271, the MPA levels were significantly lower when administered in the abdomen compared to the anterior leg during the first two weeks but the difference was not remarkable thereafter. The C_{max} was significantly different (abdomen 0.94 ng/mL versus thigh 1.65 ng/mL, (p=0.002) with a T_{max} at 22 days for the abdomen and 4 days for the thigh (p=0.06). Other PK parameters, including C_{91}, (abdomen 0.47 ng/mL versus thigh 0.41 ng/mL) were not significantly different.

Pharmacokinetics in the target population

All PK studies were conducted in healthy women which is the target population.

Special populations

Race

Study 271 was a single centre, open label, randomised, parallel group trial in which the duration of ovulation suppression, safety, and PK of 104 mg MPA administered subcutaneously to either the anterior leg or abdomen was assessed in 24 Asian women from 18 to 40 years of age. The study was conducted due to World Health Organization (WHO) findings that indicated Thai women had increased metabolism or clearance of MPA after IM injection and therefore also a faster return of ovulation (WHO 1987[8]). There were four Chinese, two Filipino, ten Indian, six Malayan and two Thai women with a mean age of 33.8 years and a mean BMI of 22.4 kg/m^2. The mean MPA serum concentration time profile showed peaking after about two weeks and sustained levels to 3 months.

The five ethnic subgroups had similar MPA concentration time profiles except for the Filipino group at Day 28 where there was one subject with an outlying measurement. The mean (and SD) serum MPA concentrations at the expected time of the next injection (Day 91) were 0.41 (0.08), 0.60 (0.23), 0.33 (0.18), 0.54 (0.15) and 0.47 (0.19) ng/mL in Chinese, Filipino, Malayan, Thai and Indian women, respectively There were no statistical differences found in PK parameters among the 5 ethnic subgroups. There was only one woman (a Malay) with a Day 91 MPA level below the 0.20 ng/mL threshold (MPA 0.146 ng/mL) but there was no evidence of ovulation in this woman as measured from other hormone levels.

[8] World Health Organization, Task force on long-acting systemic agents for fertility regulation. A multicentered, pharmacokinetic, pharmacodynamic study of once-a-month injectable contraceptives. I. Different doses of HRP112 and of Depo-Provera. *Contraception* 1987; 36(4):441-57.

In Study 272, subgroup analysis by race (one Asian, 14 Black and 27 Caucasian) found no statistical differences in PK parameters except for T_{max} which was longer in Black women (16 days) compared to White women (5 days) and Asian women (4 days) (p=0.038).

Body Mass Index

Pharmacokinetic data from the 42 women in Study 272 were analysed by body mass index (BMI) at cut offs of ≤25, >25-30, and >30 kg/m^2. There were no significant differences in PK parameters between the groups except for T_{max} which was 4 days, 17 days and 7 days in the three groups, respectively (p=0.04). When examining data by the protocol defined groups ≤28, >28-38, and >38 kg/m^2 there was a significant difference in the $AUC_{0-\infty}$ with a lower level in those with a BMI >38 kg/m^2 (p=0.039). Although there were no other statistically significant differences, the C_{91} was lower in the women with BMI>38 kg/m^2 at 0.259 ng/mL (p=0.06).

Interactions

There were no specific drug-drug interaction studies in the current Australian submission.

Exposure relevant for safety evaluation

For the 47 women enrolled In Study 265, 100% reported at least one adverse event (AE) with the most frequent being injection site reactions and headache. There were no evident trends with increasing dose.

Pharmacokinetic conclusions

Data from the three trials providing PK data on MPA after administration of DMPA-SC are summarised in Table 4.

Table 4.

Mean (SD) Pharmacokinetic Parameters of MPA After DMPA-SC Administration

Study (Ref)	Cmax (pg/mL)	tmax (day)	AUC0-91 (ng day/mL)	AUC0-∞ (ng•day/mL)	C91 (ng/mL)	t1/2,z (day)
265* (10)	0.90 (0.35)	21 (21)	41.5 (13.4)	54.0 (15.9)	0.332 (0.137)	27 (12)
271 (11)	1.29 (0.6)	13 (23)	63.9 (16.2)	118.1 (16.4)	0.441 (0.177)	91 (59)
272 (12)	1.56 (0.67)	9 (13)	66.9 (24.9)	92.8 (23.5)	0.402 (0.147)	43 (21)

* Dose was 100 mg per 0.5 mL

Following subcutaneous administration of DMPA, there was a prompt increase in serum concentrations such that levels above the reported therapeutic threshold of 0.2 ng/mL were reached within 24 hours. While the single dose PK was characterised by high inter-subject variability, there was prolonged absorption and the MPA trough concentrations on Day 91 (when the next dose would be due to be administered) were above the therapeutic threshold. The PK data showed better comparability between the studies 271 and 272 which used the proposed 104 mg/0.65 mL SC formulation, than Study 265 using the 100mg/0.5 mL IM formulation. In Studies 271 and 272, the AUC_{0-91} values obtained with the 104 mg/0.65 mL formulation were 64 ng. day/mL and 67 ng. day/mL, respectively, which can be compared to 42 ng. day/mL with the 100 mg/0.5 mL formulation used in Study 265 (the plasma exposure following the latter formulation was about 35% less).

Subcutaneous injection of DMPA-SC in the anterior thigh resulted in a higher C_{max} than in the abdomen (1.65 versus 0.94 ng/mL, p=0.002) however there were no differences in

MPA trough concentrations (C_{91}) (0.41 ng/mL versus 0.47 ng/mL respectively, p=0.44). Injection site was also assessed in Study 265 and while results looked similar there was no formal testing for difference.

Race does not appear to have any significant effect on the PK of MPA although the small numbers in each of the five Asian ethnic subgroups did not allow conclusions to be made at this level of specificity. BMI did not have a major effect on MPA PK, though with increasing BMI there was a trend to a longer time to reach peak concentration. In addition, trough concentrations were lower in obese women with BMI >38 kg/m^2 but remained above the contraceptive effect level at 0.26 ng/mL. Given this, dose adjustments based on BMI would not be necessary. This information is adequately covered in the PI.

Pharmacodynamics

The pharmacodynamics of DMPA-SC were examined in three clinical trials (Studies 265, 271 and 272) in which a total of 139 healthy women were enrolled.

Mechanism of action

The primary mechanism of action of DMPA-SC is the inhibition of ovulation. This is achieved via the inhibition of the secretion of gonadotropins (luteinising hormone [LH] and follicle-stimulating hormone [FSH]) from the anterior pituitary which, in turn, prevents follicle maturation and ovulation.

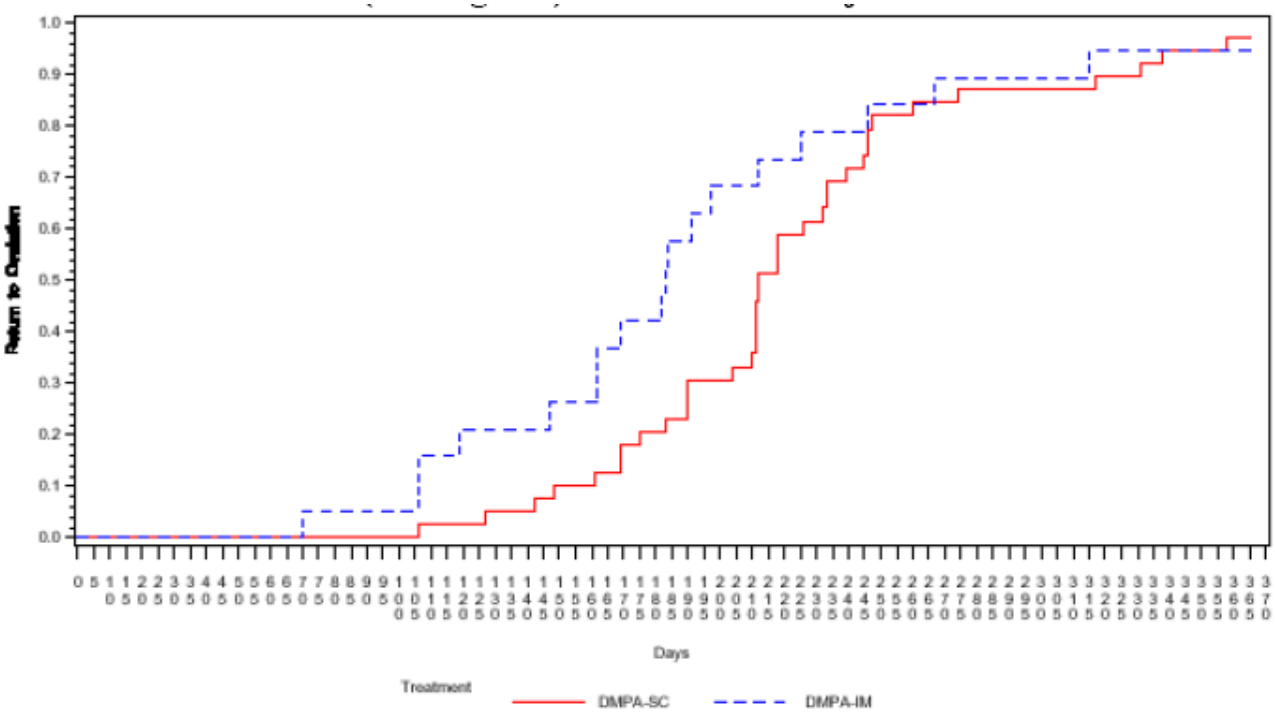
Primary pharmacology

The suppression of ovulation was primarily determined from serum progesterone levels. A serum progesterone concentration of ≥4.7 ng/mL was used as the threshold for ovulation occurrence (Aedo AR 1985). Supporting markers were serum oestrogen (E2), LH and FSH concentrations. An increase in E2 ≥150 pg/mL was indicative of ovarian follicle activity and of progesterone ≥3 ng/mL of luteal phase activity. In addition, in Study 272, daily urine samples were collected for urinary LH, oestrone glucuronide (E1-G) and pregnanediol-3-glucuronide (Pd-3-G). Ovulation based on Pd-3-G levels was defined as three consecutive visits with levels ≥3 times the average baseline value. In Study 265 (100 mg group) and Study 272, women also had vaginal ultrasounds to determine ovarian follicle growth and endometrial thickness. Blood sampling frequency during the treatment phase for hormonal levels (progesterone, E2, FSH and LH) was the same as for the PK sampling. In Study 272, hormone levels were also collected weekly from Day 141 until ovulation occurred or until Day 365.

Inhibition of ovarian function and ovulation

In Study 271, progesterone concentrations were suppressed in 23 of 24 women for at least 112 days. One Filipino woman in this group had serum progesterone of 16 ng/mL on Day 57. Other hormone levels (E2, LH, FSH) in this woman did not support ovulation and MPA level on Day 91 was also above the threshold at 0.438 ng/mL. In Study 272, after a single injection of DMPA, the first occurrence of ovulation based on serum progesterone levels was on Day 106 in the DMPA-SC group and on Day 70 in the DMPA-IM group (Figure 2).

Figure 2. Study 272. Time to return of ovulation based on progesterone levels (≥4.7 ng/mL) in Evaluable subjects.



Return of ovarian function and ovulation

In Study 272 at 12 months post a single injection, 38/39 (97.4%) women in the DMPA-SC group and 18/19 (94.7%) in the DMPA-IM group had returned to ovulating (Figure 2). The median time to return to ovulation (based on serum progesterone ≥4.7 ng/mL) was 212 days for women receiving DMPA-SC and 183 days for those who received DMPA-IM which was not significantly different (p=0.202). For subjects with evaluable urinary Pd-3-G data (64% of the DMPA-SC and 79% of the DMPA-IM groups), the median time to ovulation was 186 days and 171 days in the DMPA-SC and DMPA-IM groups, respectively, which also was not statistically different (p=0.246).

Return to ovulation was also calculated using the modified Hoogland method[9]. The time to ovulation using this method was variable and depended on the number of criteria met. When four criteria were met, the median time was 190 days and 166 days in the DMPA-SC and DMPA-IM groups, respectively. Table 5 provides a comparison between the three methods on the time to return to ovulation and demonstrates the variability in the methodologies.

[9] The modified Hoogland method uses 6 criteria based on: increase in E2, FSH peak, follicle size, follicle diameter rapid decrease, progesterone peak, and LH peak.

Table 5. Study 272. Methodology comparison (evaluable subjects) for return to ovulation

Day of First Criteria Met	DMPA-SC (N = 39)			DMPA-IM (N =19)		
	PROTOCOL		HOOGLAND	PROTOCOL		HOOGLAND
	Progesterone	Pd-3-G	4 Criteria Met	Progesterone	Pd-3-G	4 Criteria Met
Mean (SD)	218.7 (54.8)	197.1 (60.7)	187.7 (62.6)	180.2 (60.5)	176.5 (55.1)	171.7 (65.9)
Median	212	186	190	183	171	166
Min-Max	106 - 358	109 - 333	24 - 351	70 - 315	101 - 316	49 – 315
Total Reported	38	25	35	18	15	16

Notes: Progesterone levels must be ≥4.7 ng/mL; the first occurrence of Pd-3-G reaching levels that, if found, were ≥3 times its average baseline value for 3 consecutive visits
Source: Tables T5.3.2, T5.6.2.2, and T5.7.4.2

Body Mass Index

In Study 272, BMI (≤28, >28 to 38 and >38 kg/m^2) had no effect on the cumulative rate of ovulation with all women having evidence of ovulation at 12 months except one in the >38 kg/m^2 group who received DMPA-SC. The median time to ovulation return for women after a single dose of DMPA-SC appeared to be shorter in those with a higher BMI (median time of 239, 187 and 212 days in the ≤25, >25-30 and >30 kg/m^2 groups) although this was not statistically significant (p=0.232).

Race

In Study 272, the median time to return of ovulation was significantly shorter in Black women (190 days) than White women (218 days) (p=0.013). The sponsor stated that as there were more Black women in the higher BMI groups and this result may have been confounded by BMI.

Secondary pharmacology

In Study 265, the 100 mg dose group had endometrial thickness measured by vaginal ultrasound. The mean thickness between Days 63-112 post dose was similar to the control cycle follicular phase.

Bleeding patterns were assessed in Study 272 from daily diary entries using a 5 point scale[10]. It was noted that the mean percent of days in each cycle with bleeding or spotting days was 21.3% (SD 5.9) in the control cycle and this rose to 37.3% (SD39.2) at the third month post DMPA-SC. Such a rise in the percent of days with bleeding or spotting was also noted with DMPA-IM (22.9% (SD 9.6) in the control cycle and 44.7% (SD 42.2) at Month 3.

In Study 271, there was some evidence of follicular activity with serum E2 concentrations >150 pg/mL in 10 of the 24 women and LH and FSH levels remained in the early to mid follicular phase range. In Study 272, vaginal ultrasounds were conducted and the median follicle diameter during the first 3 months post injection was <10 to 10.8 mm in the DMPA-SC group and <10 to 11.2 mm in the DMPA-IM group compared to 19.9 and 20.1 mm in the DMPA-SC and DMPA-IM groups, respectively, during the control cycle.

Relationship between plasma concentration and effect

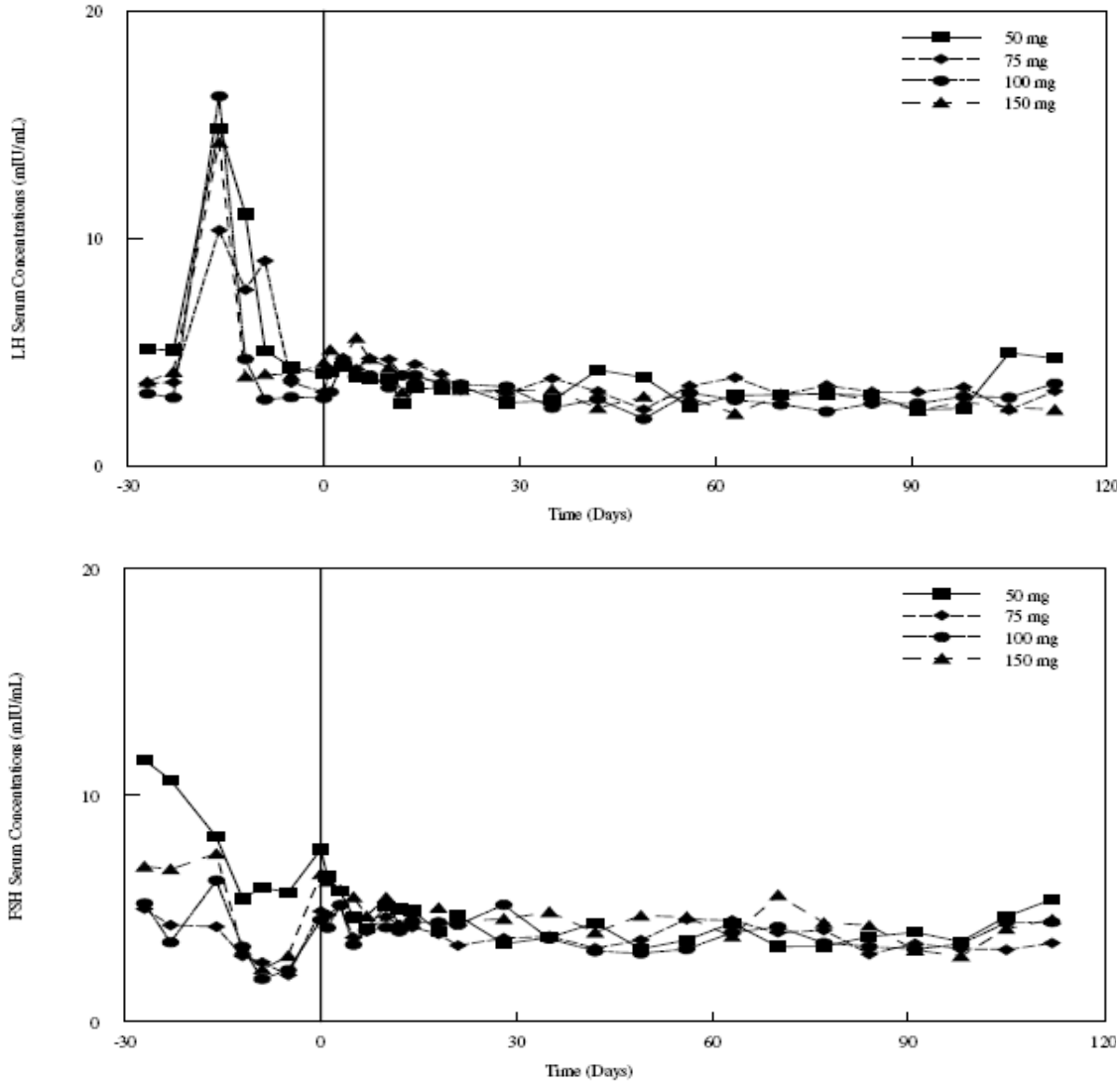
Data on concentration response relationships were not provided in the current Australian submission. The sponsor stated that serum MPA levels at or above 0.2 ng/mL are needed

[10] Bleeding pattern 5 point scale: 0 = no flow (no protection needed). one = spotting (light pad or no protection). two = bleeding with use of sanitary pads or tampons needed less than usual. 3 = bleeding, with use of sanitary pads or tampons needed about the same as usual. 4 = bleeding with use of sanitary pads or tampons needed more than usual.

to suppress ovulation in nearly all women. As levels drop below 0.1 ng/mL the contraceptive efficacy falls. Consequently, MPA trough concentrations (C_{91}) were used as a guide for dose selection in Study 265. As noted above, MPA levels at Day 91 were above the 0.20 ng/mL threshold for ovulation suppression in the 100 mg and 150 mg dose groups but had dropped below this level in a number of women in the 50 mg and 75 mg groups. The 50 mg and 75 mg doses suppressed progesterone concentrations to ≤4.7 ng/mL in 8/11 and 11/12 women respectively. In the 100 mg group, 11 of 12 women had suppressed progesterone levels, with one woman ovulating on Day 70. This subject had unusual MPA PK profile, with a high peak but rapid decline in MPA levels. In the 150 mg group, serum progesterone levels were suppressed in all 11 women. One woman dropped out and was lost to follow up in the 150 mg group.

Follicular activity was measured by serum E2 levels. Higher DMPA-SC doses resulted in greater E2 suppression. Levels of E2 in the 50, 75 and 100 mg groups were similar to the early to mid follicular phase of the control cycle. Weekly blood sampling was insufficient to capture LH and FSH peaks. There was, however, no indication of an LH or FSH peak in any dose group (Figure 3).

Figure 3. Study 265.Mean Serum LH (top graph) and FSH (bottom graph) concentration-time profiles during a control cycle and after a single dose of DPMA-SC.



In Study 272, the correlation between C_{91} values and return to ovulation was assessed and the correlation coefficient was 0.035 suggesting that the trough serum MPA concentration is not predictive of the return to ovulation.

Pharmacodynamic interactions with other medicinal products or substances

It is known that MPA is extensively metabolised in the liver by P450 enzymes and that induction of these (notably CYP3A4) would lead to an increase in MPA clearance and possibly to plasma MPA levels below the minimum effective concentration. In the Phase III contraception efficacy studies (Studies 267, 267BMD and 269), approximately 10% of women took concomitant medications with potential inducing or inhibiting effect on CYP3A4 enzymes. There were no pregnancies reported in these studies so there were no reports of a drug-drug interaction leading to method failure.

Genetic differences in pharmacodynamic response

There were no pharmacology studies which specifically examined the effects of genetic differences on the pharmacodynamics of DMPA-SC.

Clinical evaluator's conclusions on pharmacodynamics

Serum progesterone levels less than 4.7 ng/mL were the main criteria used to assess suppression of ovulation. Return to ovulation was primarily assessed by serum progesterone levels, urinary Pd-3-G and the modified Hoogland criteria. It was noted that the studies generally had weekly blood sampling which would not necessarily be frequent enough to capture the short term peaks of the supporting hormones (E2, LH, FSH).

The dose finding study (Study 265) found MPA 150 mg effective in suppressing ovulation as was MPA 100 mg if one outlier was removed. Over the 3 month dosing interval, a DMPA-SC 104 mg dose suppressed ovulation in 23 of 24 Asian women (Study 271) and all 39 evaluable women in Study 272. The only woman with increased progesterone did not show evidence of ovulation using other markers (E2, LH, FSH, MPA concentration). In Study 272, the earliest return to ovulation was at 105 days (15 weeks), the median time was 212 days. At 12 months, 97% women (38/39) had returned to ovulation.

Although there was no statistical difference between BMI groups, women with a higher BMI tended to have a shorter time to return to ovulation and this correlates with the PK findings of lower AUC and C_{min} in this group. Despite this, the 104 mg SC dose was effective at suppressing ovulation and C_{min} at the time of the next dose was above the threshold, so dose adjustment based on BMI would not be necessary.

DMPA-SC inhibited ovulation in Black and Asian women although there was one Asian woman whose progesterone level rose though ovulation was not confirmed. The subgroups of Asian women were too small in number to draw meaningful conclusions on specific nationalities. Black women did show a quicker return to ovulation than White women (190 days and 218 days, respectively) though none did so under 91 days and the sponsor stated the result may have been confounded by BMI. While this is a plausible explanation, it could not be verified as specific data were not presented.

Ovulation took a longer time to return following a SC injection compared to IM DMPA (median 212 days versus 183 days based on serum progesterone). This may be explained by the slower absorption from SC site and the apparent longer half life (35-47 day SC compared to 13-26 days IM).

Efficacy

Introduction

The contraceptive efficacy clinical trials of DMPA-SC included three Phase III studies: two open label, non-comparative, one year trials (Studies 267 and 269) and one randomised investigator blinded three year trial (Study 267BMD) that compared the effect of DMPA-SC and DMPA-IM on bone mineral density (BMD). For the endometriosis indication, there were two Phase III trials (Studies 268 and 270) which had the same design and compared DMPA-SC to the GnRH agonist leuprolide. All SC injections used the formulation proposed for marketing (104 mg/0.65 mL per injection) and were administered every three months.

Main Clinical Studies

Dose response studies

The dose selection for the Phase III contraceptive program was based on the results of pharmacology Study 265 (summarised above in the section *Relationship between plasma concentration and effect*).

Evaluator's comments on the dose-ranging study

The 50 and 75 mg doses were not effective at suppressing ovulation in all women. The 150 mg dose suppressed ovulation in all women but the PK analysis indicated that the MPA levels were higher than required. The 100 mg dose suppressed ovulation in all women when data from one outlier was removed. This dose also maintained the MPA concentration above the threshold level of 0.20 ng/mL at Day 91. The sponsor suggested that the woman with the unusual MPA PK profile may have been due to an injection close to or into a blood vessel. They report this as the first such PK profile in a database of 200 single injections and 300 multiple injections of Depo-Provera IM or Lunelle IM and SC. This translates to a potential risk of one in 200 (0.5%) of method failure which, while not ideal, is acceptable for such a contraceptive. From this study it was concluded that 100 mg is the most appropriate dose to use in the Phase III program and the pharmacodynamic effect of this dose at suppressing ovulation was further confirmed in Studies 271 and 272.

Main (pivotal) Studies

Study 267 – Contraceptive Efficacy

Methods

Study 267 was a 12 month open label, non-comparator study to examine contraceptive efficacy, safety and subject satisfaction with DMPA-SC in 18-49 year old women. The study was conducted between 2001 and 2002 in 74 centres in Brazil, Canada, Chile, Mexico, Peru and the USA. Women received MPA 104 mg/0.65 mL packed in a prefilled syringe and given subcutaneously to the anterior thigh or abdomen every three months for one year. The first dose was given in the first five days of a normal menstrual cycle and then every 91 ± 7 days. Subjects completed daily diaries to record bleeding and spotting as well as unprotected intercourse[11].

Study participants

For inclusion, women were sexually active, desired long term contraception, had a recent negative pregnancy test and were menstruating regularly in the three months prior to enrolment. Women were excluded if they had: oral contraceptives, hormonal intrauterine devices (IUDs) or contraceptive implants within two months or DMPA-IM within 10

[11] There is no mention whether these diaries were electronic. The evaluator assumes they were hard copy.

months; abnormal cervical cytology within 12 months; breast cancer history or suspicion; history of thrombotic event; undiagnosed vaginal bleeding; suspected pregnancy; history of drug abuse or alcoholism within 5 years; uncontrolled hypertension (systolic blood pressure (SBP) >180 mmHg, diastolic blood pressure (DBP) >110 mmHg); active hepatic or renal disease (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total bilirubin (BR) >2.5 times upper limit of normal, or creatinine >1.8 mg/dL); poorly controlled insulin dependent diabetes mellitus (IDDM) or non-insulin dependent diabetes mellitus (NIDDM); tubal ligation or diagnosis of infertility or sterile partner; or taking the anticancer agent aminoglutethimide.

Outcomes/endpoints and statistical methods

The primary efficacy endpoint was treatment failure cumulative pregnancy rate at one year. This was defined as a positive urine pregnancy test prior to the next scheduled injection. Sites were provided with lateral flow immunoassay urine pregnancy tests. Secondary endpoints were incidences of amenorrhoea, irregular bleeding, AEs and subject satisfaction with the treatment.

Sample size: The sample size was set to gather data on 5000 cycles (months) of experience with DMPA-SC and to include at least 200 subjects (≤35 years) for one year. Inclusion of 500 women was planned and with an assumed drop-out rate of 12% per clinic visit or 40% for one year, a sample size of 750 subjects was chosen.

Statistical methods: Analysis was based on the "intent to treat " (ITT) population which was all women who received at least one dose of study medication and had at least one visit after the first dose. The incidence of treatment failure cumulative pregnancy was assessed by calculating the rate and 95% confidence interval (CI) using the life table method and Pearl Index.[12]

Results

Participant flow: There were 738 women enrolled and of these 722 women were treated (610 of these women were aged ≤35 years). Of the 722 women, 489 (67.9%) completed the study (407 ≤35 years). There were two women who did not return for a study visit after dosing and therefore the ITT population included 720 women. Of the 233 subjects who discontinued, 98 withdrew due to AEs, 78 withdrew their consent, 49 subjects were lost to follow up and 8 instances were due to protocol violations. There were 14/722 (1.9%) subjects who did not meet the eligibility criteria and the most common reason was not menstruating regularly in the three months prior to enrolment.

Conduct of study: The study protocol was amended eight times. Amendment 1 was prior to enrolment and resulted from FDA advice. It added the exclusion of women with breast cancer or recent contraception and subgroup analyses (medications metabolised by CYP3A4, self injection and barrier contraception). Amendment 2 allowed subjects to self inject at home during the second six months of the study after training and demonstrating self-injecting at the study office. The other six amendments were site or substudy specific.

Baseline data: The mean age of the participants was 28.2 years with 84.5% being 35 years or younger. Most were White (485/722, 67.2%) and the mean BMI was 25.3 kg/m^2. The average number of days of bleeding per cycle was 4.8 days with an average cycle

[12] The life table method of analysis provides a cumulative failure rate showing the proportion of women whose method of contraception failed within the specified time period.
The Pearl Index is defined as the number of pregnancies per 100 woman-years of exposure, where the numerator is the number of failures and the denominator is a function of each woman's total months of drug exposure during the study (3 times the number of injections received).

length of 28.9 days. Two thirds (484/722) of the women took concomitant medications during the study, the most frequent being paracetamol (19.7%), ibuprofen (13.6%), ascorbic acid (5.8%), ergocalciferol (5.3%), retinol (5.1%), riboflavin (5.0%) and nicotinamide (5.0%). There were 91/722 (12.6%) women who took a medication metabolised by the CYP3A4 pathway, these included fluticasone propionate, azithromycin, clarithromycin, erythromycin, and prednisone. CYP3A4-inducing medications were taken by 7.5% (54/722) and CYP3A4-inhibiting medications were taken by 8.3% (60/722) of the subjects. Five women received oestrogen products to control excessive bleeding.

There were 497/722 (68.8%) women who received four DMPA-SC injections, with 384/722 (53.2%) women who gave themselves the injection on at least one occasion and 73/722 (10.1%) who were able to self-inject at home.

Compliance: Compliance, as measured by injections being given within the specified window of 91 days ± 7 days, was high with over 94% of injections being administered within this window at Month 3, 6 and 9. There were four subjects who received the injection in the upper arm. For the 73 women who injected at home, three reported doing so outside the specified window.

Outcomes and estimation

Primary outcome: Of the 720 subjects with data, there were no pregnancies so the primary efficacy endpoint of treatment failure cumulative pregnancy rate at one year was 0% and the Pearl Index was 0 pregnancies per 100 women years. Confidence intervals were not calculated in the sponsor's *Clinical Study Report* (CSR). There was one inconclusive urine pregnancy test which was negative on repeat testing. Overall there were 7209 women cycles of exposure and 5616 women cycles of exposure with risk of pregnancy (excluding cycles with use of barrier contraception at least sometimes and no intercourse).

There was one spontaneous abortion reported in a 20 year old woman. It occurred three weeks after her first dose of study medication (negative pregnancy test at this time). Pathology reported debris and necrotic decidua and the investigator reported the subject to be six weeks pregnant at the time and it was believed she was pregnant at the time of study enrolment. There were 54/720 (7.5%) women who took concomitant medications that induced CYP3A4 enzymes. There was no loss of contraceptive efficacy as there were no reported pregnancies.

Return to Ovulation and Fertility Substudies: The sponsor's *Clinical Overview* provided some information about these substudies. There were 15 women followed for one year at the end of Study 267 with the median time to serum progesterone ≥4.7 ng/mL being 291 days and 12 (80%) women having such levels within the 12 month follow up period. There were ten women who desired to become pregnant after leaving Study 267 and they were followed with a urine pregnancy test 120 days after the last injection and a telephone call 365 days later. Six of the ten were contactable, all had had unprotected intercourse and one was pregnant 310 days after the last DMPA-SC dose.

Efficacy summary

DMPA-SC was effective with no pregnancies reported in 720 women in 7209 cycles of exposure (5616 cycles when barrier contraception and no intercourse were excluded). Due to the fact that the full study reports were not available for evaluation, the small numbers and self-selected nature of the subjects, conclusions cannot be drawn on the effect on treatment on return to ovulation or fertility.

Study 269 – Contraceptive Efficacy

Methods

Study 269 was a 12 month open label, non-comparator study to examine contraceptive efficacy, safety and subject satisfaction with DMPA-SC in 18-49 year old women. The study was conducted between 2001 and 2002 at 64 sites in Bulgaria, Estonia, Latvia, Lithuania, Poland, Russia, Romania, UK, Norway, Pakistan and Indonesia. The objectives, design and study medication were the same as Study 267. All study participants were followed for 120 days after the last dose for possible pregnancies. Included in this study was an endometrial biopsy substudy in Russian women.

Study participants

Inclusion and exclusion criteria were the same as in Study 267, the only difference being the exclusion of women with a significant risk of osteoporosis (as determined by the investigator) and those receiving concomitant medications with cytochrome P450 inducing effects.

Outcomes/endpoints and statistical methods

As in Study 267, the primary efficacy variable was the treatment failure cumulative pregnancy rate at one year based on the ITT population.

Sample size: As in Study 267, sample size was set at 5000 cycles of DMPA-SC and 200 women 35 years or younger for one year. Assuming a drop out of 40% over one year 850 subjects were planned to be enrolled.

Statistical methods: The statistical methods were the same as in Study 267.

Results

Participant flow: There were 1067 women registered. Two of these did not receive the study medication and therefore the ITT population was 1065 with 739 (69.4%) aged 35 years or younger. Overall, 856/1065 (80.4%) completed the study which included 539 women ≤35 years. Of the 209/1065 (19.6%) who prematurely discontinued, 116 (10.9%) withdrew consent, 56 (5.3%) withdrew due to adverse events and 32 (3%) were lost to follow up. Protocol deviations relating to inclusion/exclusion criteria included 13 subjects with abnormal Pap smear results, two with abnormal mammograms and 17 subjects who were not menstruating regularly. In addition, six subjects did not have a visit after the first dose. The ITT population for efficacy analysis was therefore set at 1059.

Conduct of study: The study protocol was amended four times. Amendment 1 was issued prior to subject enrolment and included a reduction of sample size from 1300 to 850, removal of lipid and coagulation profiles and resultant blood samples, and the addition of an endometrial biopsy substudy. The other three amendments were country specific.

Baseline data: The mean age of the women was 32.2 years with 69.4% under the age of 35. Some 97.9% were White and the mean BMI was 23.2 kg/m^2. The average number of days of bleeding per cycle was 5.1 with an average cycle length of 28.8 days. Over the course of the study, 33.5% of subjects took a concomitant medication, the most common being paracetamol, ascorbic acid and acetylsalicylic acid. There were 31/1065 (2.9%) women who took a medication metabolised by the CYP3A4 pathway and 11/1065 (1%) took a drug that was a CYP3A4 inducer. Five subjects took oestrogen products for menstrual bleeding regulation.

Overall, 856/1065 (81.2%) subjects received four injections of DMPA-SC; 61.6% of the women self-injected at least once and 19.5% were able to do self-administer at home.

Compliance: As in Study 267, compliance was high with over 92% of injections administered within the specified time range.

Outcomes and estimation

Primary outcome: There were no reported pregnancies in the 1059 women (follow up data was not available for six women) so the treatment failure cumulative pregnancy rate was 0% and the Pearl Index was 0. No confidence intervals were calculated in the CSR. Overall, there were 11,472 women cycles of exposure with 10,407 cycles of exposure with risk of pregnancy (excluding months when barrier contraception was used or no intercourse occurred). No contraception failure was noted in the 11/1065 (1%) women who took a CYP3A4 inducing medication (including fluconazole and azithromycin).

Return to Ovulation and Fertility Substudies: There were 18 women leaving Study 269 because they wished to become pregnant. A follow up of 15 of them found one subject pregnant 443 days after her fourth DMPA-SC dose.

Efficacy Summary

DMPA-SC was effective as there were no reported pregnancies. In addition, efficacy was maintained in the 61.6% of women who self injected at least once.

Study 267BMD – Contraceptive Efficacy and BMD

Methods

Study 267BMD was a three year substudy of the primary 12 month contraception efficacy trial Study 267. It was a randomised, investigator blinded trial of DMPA-SC and DMPA-IM in women aged 18 to 35 years with the primary objective to evaluate BMD changes at one, two and three years relative to baseline. In addition, BMD changes were evaluated one year after ceasing DMPA for those continuing in the study off treatment in Year 3. Other secondary objectives included contraception efficacy, safety and PK of MPA (C_{min} levels). This study was conducted between 2001 and 2004 at three sites in Brazil, nine sites in Canada and 36 sites in the USA.

Subjects were randomised via an interactive voice response system (IVRS) in a 1:1 ratio to receive DMPA-SC 104 mg/0.65 mL subcutaneously (to the abdomen or anterior thigh) or DMPA-IM 150 mg IM (buttock[13]) every three months up to three years. Medications were supplied in prefilled syringes. To maintain evaluator blinding, independent staff administered the injections and staff and subjects were instructed not to reveal or discuss the treatment assigned. The study was unblinded centrally at the end of Year 2 for analysis, though the sponsor stated it remained investigator blinded in Year 3. There was no set requirements for medications that may affect BMD measurements in the study.

After a baseline visit which included a BMD assessment, subjects had three monthly study visits to Month 36 with annual BMD assessments of the lumbar spine (L1-4) and femur. Urine pregnancy tests were performed at each visit and lateral flow immunoassays were supplied to the study sites. PK samples for MPA C_{min} determination were taken at 6, 12 and 24 months. Bleeding pattern diaries were kept by each subject during the first two years of the study.

[13] While the CSR states administration could be in the upper arm or buttock it lists upper arm administration as a protocol deviation so the evaluator assumed this reference to upper arm injection site is an error.

Study participants

Study inclusion criteria were the same as in Study 267 with the exception that women were younger (18 to 35 years). Exclusion criteria were the same as in Study 267 but with the additional exclusion of women with an increased risk of osteoporosis as defined by a T-score[14] <-1.0 or history of pathological or compression fracture.

Outcomes/endpoints and statistical methods

The primary efficacy endpoint was the treatment failure cumulative pregnancy rate at two years. The primary safety variable was the percent change from baseline in BMD after two years of treatment. BMD change at one and 3 years were secondary endpoints. The percent change was calculated for femur neck, femur total and spine total. BMD was assessed using dual-energy X-ray absorptiometry (DXA) measurements. The sponsor ensured quality control of the DXA scans by including training of the DXA technologists and a centralised analysis and reporting of all BMD scans.

Sample size: A sample size of 100 subjects in each treatment group was determined to give 80% power to detect a 2% difference in the percent change of BMD between the two treatment groups at a significance level of 0.049 at the end two years and assuming a standard deviation of 5%. Allowing for a drop out of 60% in two years, the final sample size was 250 subjects per group.

Statistical methods: As in Study 267 and 269, the primary efficacy variable was treatment failure cumulative pregnancy rate at two years, calculated using the life table method and Pearl Index. With respect to BMD, the study was designed to test superiority of DMPA-SC to DMPA-IM in reducing the BMD loss compared to baseline after two years of treatment. Two-sided statistical testing was done. Methods included analysis of variance (ANOVA), Kruskal-Wallis, Wilcoxon signed rank and chi-square tests. An interim analysis was conducted at one year with a significance level of 0.001 (at two years the significance level was 0.049). There was no p value correction for the third year analysis. The ITT population for efficacy included women who had received one dose of medication and had returned for at least one study visit.

Results

Participant flow: A total of 535 subjects were enrolled and of these 266 received DMPA-SC and 268 were given DMPA-IM (one did not receive study medication). Of these, 116 (43.6%) in the DMPA-SC group and 109 (40.7%) in the DMPA-IM group completed two years of treatment. Of the 150/266 (56.4%) subjects receiving DMPA-SC who prematurely discontinued, 43 (16.1%) were lost to follow up, 46 (17.3%) had adverse events, 50 (18.8%) withdrew consent and there were 11 (4.1%) protocol violations. Premature discontinuations were similar in the DMPA-IM group (59.3%) with 22.2% due to AEs, 13.8% withdrawing consent, 21.6% lost to follow up and 1.9% protocol violations. There were 84 DMPA-SC, 71 DPMA-IM and 6 "no treatment" subjects who continued into Year 3, with 66, 56 and 6, respectively, also finishing the third year of the study. There were 10 subjects (four DMPA-SC and six DMPA-IM) that did not meet the exclusion criteria for osteoporosis.

Conduct of study: The study protocol had a number of amendments. The main one was Amendment 10 which extended the study from two to three years and also allowed data collection at the end of Year 3 for those not continuing on study medication.

[14] T-score was defined as the number of standard deviations from the mean BMD of a young normal Caucasian female reference population as described by the National Health and Nutrition Examination Survey.

Baseline data: Baseline characteristics were similar in the DMPA-SC and DMPA-IM groups: mean age 25.9 versus 25.8 years; White 61.3% versus 63.4%; and mean BMI 26.1 versus 26.4 kg/m^2. Baseline bleeding and concomitant medication use during the study were also similar between the groups (DMPA-SC versus DMPA-IM: 79.7% versus 75.4%). CYP3A4 metabolised medications were taken by 17.3% and 13.4% of the DMPA-SC and DMPA-IM groups, respectively, with CYP3A4 inducing medications taken by 10.9% (29/266) and 6.7% (18/268) of subjects, respectively. The use of calcium supplements (about 5% in both groups) and ergocaliferol (14.7% versus 16.4%) were also similar. Exposure to study medication was also similar with eight injections received by 15.4% and 18.3% and twelve injections by 25.2% and 21.3% of the DMPA-SC and DMPA-IM subjects, respectively.

Compliance: Over 92% of subjects received their study medication within the scheduled window of 91 ±7 days. Three DMPA-SC subjects received their injection in the upper arm and one DMPA-IM subject received the drug SC. One DMPA-IM subject received DMPA-SC at Month 3 and discontinued the study and two DMPA-IM subjects received their injection in the upper arm. There were also three DMPA-SC and four DMPA-IM subjects who had their final visit at 24 month conducted by the unblinded staff member who had administered the injections.

Outcomes and estimation

Primary outcome: There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the DMPA-SC women became pregnant while one of the DMPA-IM women became pregnant and discontinued the study at 21 months. The treatment failure cumulative pregnancy rate for DMPA-SC was 0% compared to 0.8% for DMPA-IM (95% CI: 0.0 to 2.37%). The Pearl Index was 0 for DMPA-SC compared to 0.28 (95% CI: 0.0 to 0.83) pregnancies per 100 women years exposure for DMPA-IM. At two years, there were 4344 and 4281 women cycles of exposure and 3565 and 3442 women cycles with risk of pregnancy in the DMPA-SC and DMPA-IM groups, respectively. There were no pregnancies in Year 3 so the treatment failure pregnancy rate remained the same and the Pearl Index was 0 for DMPA-SC (5241 women cycles) and 0.24 (95% CI 0.0, 0.70) for DMPA-IM (5067 women cycles). The single subject who became pregnant had a BMI of ≤25 kg/m^2 and did not take any concomitant medication or CYP3A4 metabolised medications.

Results on the effect on BMD are under *Safety* below.

Efficacy Summary

DMPA-SC showed contraceptive efficacy over two years in 266 women and 4344 cycles of exposure (3565 cycles excluding those when barrier contraception was used or there was no intercourse) with no reported pregnancies. This efficacy was greater than DMPA-IM where there was one pregnancy with a Pearl Index of 0.28 pregnancies per 100 women years (95% CI: 0.0, 0.83).

Study 268 - Endometriosis Efficacy

Methods

Study 268 was a Phase III randomised, investigator blinded, multicentre study of DMPA-SC and leuprolide in women with signs and symptoms of endometriosis. The primary objective was the assessment of equivalence in the reduction of endometriosis associated pain. The primary safety objective was the demonstration of superiority of DMPA-SC over leuprolide for minimising BMD decline after six months of treatment. Secondary objectives included changes in quality of life and time to symptom return after the end of therapy.

This study was conducted at 43 centres in the US and 7 centres in Canada between 2001 and 2003.

The study included six months of randomised treatment and 12 months of follow up on neither drug. After a screening visit, subjects were randomised on Visit 1 and then had monthly visits to Month 6 and follow up visits at Months 9, 12, 15 and 18 together with monthly telephone contact. A daily endometriosis-impact diary was kept. BMD was assessed every six months using DXA scan.

Subjects were randomised in a 1:1 ratio to receiver leuprolide or DMPA-SC. Leuprolide acetate is a synthetic analogue of gonadotropin-releasing hormone (GnRH) and 11.25 mg was given by IM injection (gluteal site). DMPA dose was 104 mg/0.65 mL given by SC injection (anterior thigh or abdomen). Both were administered using prefilled syringes every three months (91 ±7 days) starting within the first five days of a normal menstrual cycle. Washout from hormonal agent was required: two months for oral contraceptives, six months for danazol and twelve months for GnRH agonists or DMPA-IM. All subjects were given elemental calcium tablets (500 mg daily). The study was investigator blinded and all injections were given by an independent person. Subjects and clinical staff were instructed not to discuss the route of administration.

Study participants

Inclusion criteria were: women 18 to 49 years old; willingness to use non-hormonal barrier contraception for 18 months; persistent symptoms of endometriosis diagnosed by laparoscopy (and preferably confirmed by a biopsy); pain returning to previous level within 30 days and lasting at least three months after diagnostic laparoscopy (if longer since laparoscopy then other sources of pain were to be excluded; symptoms and total pelvic score of at least six from the five categories with a score of at least two for dysmenorrhoea, dyspareunia and pelvic pain (if not sexually active the total score was four with at least two in dysmenorrhoea and pelvic pain); normal Pap smear within six months; normal mammogram within twelve months if ≥35 years; and having a uterus and at least one functioning ovary.

Exclusion criteria were: pregnancy or breastfeeding; breast cancer or suspicious mammogram; hysterectomy; current or recent use of hormonal agents (see washout requirements above); BMD below acceptable criteria (lumbar and femur T score of <-1.0) or history of pathological or compression fracture; abnormal cervical cytology within 6 months; any disease which could produce pelvic pain (including inflammatory bowel disease, interstitial cystitis or fibromyalgia); active or history of hepatic or renal disease; history of severe virilisation from a medication or an endocrine disorder; history of thrombotic event; anticoagulant or drug therapy which could suppress the hypothalamic-pituitary-adrenal axis within six months; uncontrolled hypertension; poorly controlled IDDM or NIDDM; undiagnosed vaginal bleeding; and taking aminoglutethimide.

Outcomes/endpoints and statistical methods

The primary efficacy endpoint was the patient response to treatment using 5 pain categories (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration) which were evaluated using a 3 point score (modified Biberoglu and Behrman), with 0 for no discomfort to 3 for severe pain. A positive response was defined as an improvement of at least one point in the score after six months of treatment compared to baseline. For treatment equivalence, improvement in at least 4 of the 5 categories needed to be equivalent at six months. After discussion with regulatory authorities a total (or composite) score (all 5 categories) was used as a global measure of improvement with a mean decrease of 4 points considered clinically meaningful. Secondary endpoints included

the Endometriosis Health Profile-30 (EHP-30)[15] and the Short Form-36 (SF-36)[16] for quality of life (QOL), Kupperman Index for hypoestrogenic symptoms, changes in hormone levels (oestrogen, progesterone and sex hormone-binding globulin (SHBG)). All BMD scans were analysed and reported centrally.

Sample size: There were 105 subjects required per group to complete six months of treatment for the study to have an 80% power ($\alpha = 0.04$) to detect equivalence to within 20%. Assuming a drop out rate of 35% after six months, 160 subjects per group were required. To test the superiority of DMPA-SC over leuprolide on changes in BMD, 100 subjects per group gave the study 80% power ($\alpha = 0.05$) to detect a 2% change in BMD assuming a standard deviation of 5%.

Statistical methods: Equivalence in response rates was assessed using a non-inferiority design with the non-inferiority limit set at 20% and established if the lower bound of the 95% CI for the difference in proportion of subjects improving between DMPA-SC and leuprolide was greater than -20%. The sponsor did not provide a reason for why 20% was chosen for the non-inferiority limit. As 4 of 5 symptoms/signs were used for the non-inferiority criteria, to preserve the Type I error rate of 0.05, each of the 5 symptoms/signs endpoints was assessed at $\alpha = 0.04$ and 96%, 2-sided CIs were calculated. A p-value was calculated to test the null hypothesis DMPA-SC % improved – leuprolide % improved was less than or equal to -20%. Treatment equivalence was concluded when $p<0.02$. Statistical tests included ANOVA, chi square tests and Cochrane Mantel Haenszel test. Efficacy analysis was conducted on both the ITT population (at least one dose of study medication), the ITT population with last observation carried forward (LOCF) and the Evaluable population (received all three injections within seven days of the expected visit date).

Results

Participant flow: Of the 274 enrolled women, 136 received DMPS-SC and 138 received leuprolide (ITT population). There were 65 (47.8%) DMPA-SC and 77 (55.8%) leuprolide subjects who received their Month 3 injection and had their 6 month visit within the specified time window (±7 days) (Evaluable population). Premature discontinuations were higher in the DMPA-SC group than in the leuprolide group (35.3% versus 26.1%) although discontinuations due to AEs were similar (6.6% and 6.5% respectively). Discontinuations rose during the 12 month follow up to 58.0% and 56.9% in the DMPA-SC and leuprolide groups, respectively.

[15] **EHP-30.** The Endometriosis Health Profile (EHP) is a Health Related Quality of Life (HRQoL) patient self-report patient-reported outcomes (PRO), used to measure the wide range of effects that endometriosis can have on women's lives. The EHP consists of a core instrument, available as either a long-form 30 item instrument (the EHP-30), or the short-form (EHP-5) PRO. The core instruments have five scale scores covering: Pain (11), Control and powerlessness (6), Social support (4), Emotional well-being (6), Self-image (3). Numbers in brackets represent the number of items in each scale of the (long-form) core EHP-30. In addition, there is the option of deploying alongside the core instrument six supplementary modules, a total of 23 items.

[16] The **SF-36** is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

There were 43 subjects (22 DMPA-SC and 21 leuprolide) who did not meet the endometriosis pain criteria at either the baseline or the randomisation visit and one leuprolide subject who had no scores and was discontinued. There were a variety of other protocol deviations including two women (one from each treatment group) with abnormalities on mammogram, one leuprolide women with a hysterectomy, six DMPA-SC and eight leuprolide subjects with a T-scores <-1.0 at screening; one DMPA-SC with interstitial cystitis and one leuprolide with irritable bowel syndrome. There was also one leuprolide subject who received DMPA-SC at randomisation and she was withdrawn from the study.

Conduct of study: The study protocol was amended twice. Amendment 1 was implemented prior to any enrolments and included changes to the definition of the endometriosis composite score, allowing endometriosis diagnosis by laparoscopy to be within 42 months and making BMD decline a primary safety endpoint. Amendment 2 removed follow up of subjects for 12 months on study completion. The study only enrolled 274 of the planned 320 patients. Study blinding was broken in two subjects, one DMPA-SC through conversation and one leuprolide due to an SAE.

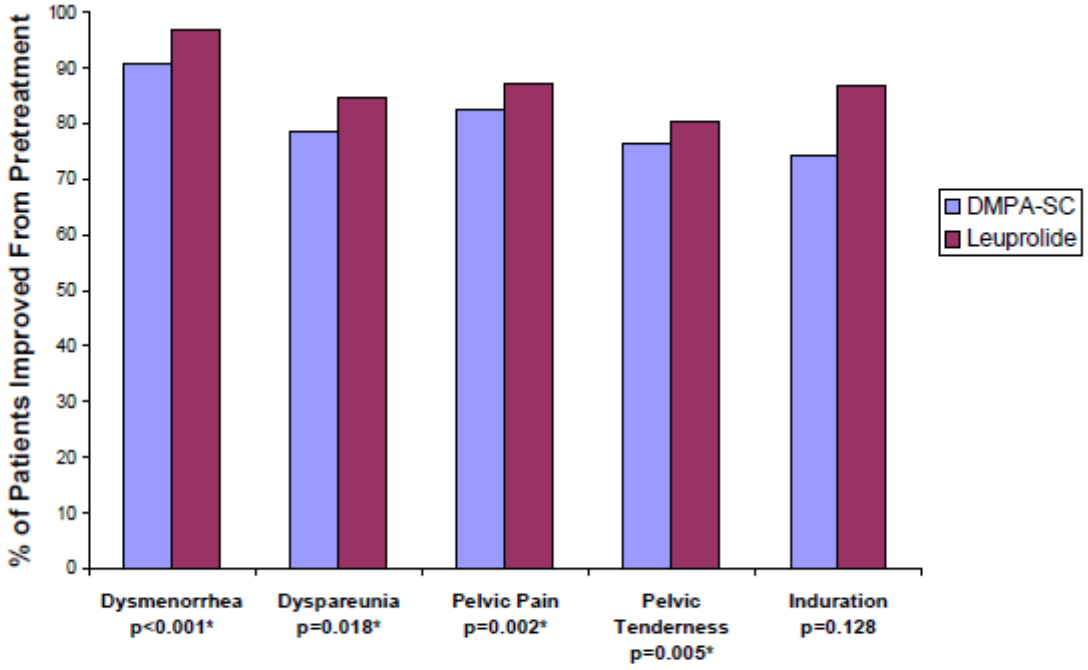
Baseline data: Women in the DMPA-SC were younger than in the leuprolide group (29.1 years compared to 32.1 years, p<0.001) but most women were White in both groups (90.4% versus 82.6%) and all had similar mean BMIs (25.8 versus 27.1 kg/m^2). The pretreatment signs and symptoms of endometriosis were similar between groups with a mean composite score of 10.0 and 10.3 in the DMPA-SC and leuprolide groups respectively. The groups were similar with respect to bleeding history, medical history, and histological evidence of endometriosis (present in 59.6% and 58.0%, respectively). Medication use before start the study was high (97.8% of each group) and included a high use of analgesics and continued as such during the study with similar use between groups. Calcium (as per protocol) and ergocalciferol use increased during the study.

Compliance: There were 31/136 (22.8%) and 20/138 (14.5%) who received one injection and 105/136 (77.2%) and 118/138 (85.5%) who received two injections of DMPA-SC and leuprolide, respectively. At least 92% of the injections were given within the specified time window.

Outcomes and estimation

Primary outcome: For the ITT population at Month 6, the reduction in 4 of the 5 components (dysmenorrhoea, dyspareunia, pelvic pain, and pelvic tenderness) were statistically "equivalent" or non-inferior (p<0.02) (Figure 4). Although the proportion of subjects responding was greater in the leuprolide group than in the DMPA-SC group for all 5 symptoms, only the induration response did not meet the non-inferiority criteria (p=0.128) (74.2% DMPA-SC versus 86.7% leuprolide). At Month 18, the reduction in all 5 symptoms and signs was statistically non-inferior.

Figure 4. Study 268. Percent of patients improved from pretreatment at month 6 (ITT population)



* The p-value tests the null hypothesis DMPA-SC % improved – leuprolide % improved ≤ -20%. Treatment equivalence was concluded when p<0.02.

Abbreviations: ITT = intent to treat, EOT = end of treatment

For the Evaluable population, the reduction in dysmenorrhoea, pelvic pain and pelvic tenderness were statistically non-inferior, however DMPA-SC had less effect on dyspareunia and induration with non-inferior criteria not being met (Table 6). In an analysis of the ITT population with the last observation carried forward (LOCF), statistical non-inferiority was found only for pelvic tenderness (Table 7). This analysis may be subject to bias from differential withdrawal rates (35.3% of the DMPA-SC group and 26.1% of the leuprolide group).

Table 6. Study 268. Signs and symptoms of endometriosis: response* in individual components at 6, 12 and 18 months (Evaluable population).

Component / Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea						
Month 6 (EOT)	65	57 (87.7)	75	73 (97.3)	0.010§	-18.85, -0.44
Month 12	45	32 (71.1)	51	33 (64.7)	0.003§	-13.14, 25.95
Month 18	34	23 (67.6)	34	20 (58.8)	0.007§	-15.11, 32.75
Dyspareunia						
Month 6 (EOT)	47	37 (78.7)	59	51 (86.4)	0.050	-23.03, 7.59
Month 12	31	26 (83.9)	35	30 (85.7)	0.020	-20.06, 16.38
Month 18	27	25 (92.6)	21	17 (81.0)	<0.001§	-8.79, 32.07
Pelvic Pain						
Month 6 (EOT)	63	52 (82.5)	76	66 (86.8)	0.005§	-16.96, 8.35
Month 12	45	34 (75.6)	51	35 (68.6)	0.002§	-11.82, 25.68
Month 18	35	28 (80.0)	34	29 (85.3)	0.053	-23.97, 13.83
Pelvic Tenderness						
Month 6 (EOT)	63	50 (79.4)	73	62 (84.9)	0.014§	-19.12, 7.99
Month 12	45	34 (75.6)	50	35 (70.0)	0.003§	-13.17, 24.28
Month 18	33	24 (72.7)	34	22 (64.7)	0.006§	-15.16, 31.20
Induration						
Month 6 (EOT)	50	37 (74.0)	55	50 (90.9)	0.336	-31.94, -1.88
Month 12	36	29 (80.6)	38	33 (86.8)	0.055	-23.91, 11.34
Month 18	26	23 (88.5)	26	25 (96.2)	0.046	-22.72, 7.34

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment.
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
Abbreviations: CI = confidence interval, EOT = end of treatment

Table 7. Study 268. Signs and symptoms of endometriosis: response* in individual components at 6 months (ITT-LOCF analysis).

Component	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea	135	102 (75.6)	137	126 (92.0)	0.206	-25.39, -7.44
Dyspareunia	100	66 (66.0)	108	87 (80.6)	0.185	-27.05, -2.06
Pelvic Pain	134	90 (67.2)	136	109 (80.1)	0.093	-23.89, -2.08
Pelvic Tenderness	134	90 (67.2)	133	97 (72.9)	0.005§	-17.26, 5.73
Induration	105	67 (63.8)	101	83 (82.2)	0.394	-30.78, -5.95

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6).
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, CI = confidence interval, EOT = end of treatment

A clinically meaningful composite score reduction (of at least 4 points) was found every month through to Month 18, in both groups. The mean change at Month 6 was -6.2 in the DMPA-SC group and -7.7 in the leuprolide group which was a statistically significant change from baseline in both groups ($p<0.001$) and the improvement with leuprolide compared to DMPA-SC was significantly different (95% CI for the difference 0.5 to 2.6) The results were similar for the Evaluable population with a mean change of -6.4 for DMPA-SC and -7.9 for leuprolide at Month 6 (95% CI for the difference 0.3, 2.8). While the mean change from baseline remained statistically significant, the ITT-LOCF analysis showed greater reduction in symptoms/signs with leuprolide (-4.9 versus -6.9 with a 95% CI for the difference of 1.0, 3.0).

When dyspareunia was excluded from the composite score at Month 6, the mean change in composite score for the ITT population was -4.8 for DMPA-SC and -6.0 for leuprolide, both significantly different from baseline ($p<0.001$). A significantly greater effect with leuprolide was also noted (95% CI for the difference 0.4, 1.9). The effect was still noticeable at 18 months (composite score reduction -3.7 and -3.9, respectively). The results were very similar for the Evaluable population.

Subgroup analyses were carried out by BMI category (≤25, 25-≤30, >30 kg/m^2), race, and age (<25, 25-≤35, >35 years). There were no notable findings except that for Black women the mean composite score reduction (5.0 points) was not significant for DMPA-SC ($p=0.125$) while it was significant for leuprolide (9.3 points). It was noted that the sample size was very small, 10 and 15 women, respectively.

Secondary Outcomes: The median time to first occurrence of symptom worsening (dysmenorrhoea, dyspareunia or pelvic pain) during the 12 month follow up period was 96 to 101 days for DMPA-SC and 96 to 106 days for leuprolide group.

Quality of life (QoL) was assessed by the EHP-30 and the SF-36. There were significant improvements for both treatment groups in the items of pain, control and powerlessness, social support, emotional well-being, self image and intercourse on the EHP-30 for the ITT population (Table 8) and the Evaluable population. Improvement in QoL was also seen from analysis of the SF-36 with improvement in scores continuing to 18 months (Table 9).

Table 8. Study 268. Endometriosis Health Profile-30. Mean responses* and test changes from randomisation (ITT population)

EHP-30 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Pain‡	Total reported	133	104	49
	Mean (SD)	49.02 (16.71)	21.68 (23.06)	29.55 (22.12)
	T-Test of change from randomization		<0.001†	<0.001†
Control and powerlessness	Total reported	133	104	49
	Mean (SD)	61.09 (23.80)	27.62 (29.23)	33.84 (29.76)
	T-Test of change from randomization		<0.001†	<0.001†
Social support	Total reported	134	104	49
	Mean (SD)	49.81 (23.45)	30.95 (27.67)	29.97 (26.97)
	T-Test of change from randomization		<0.001†	<0.001†
Emotional well-being‡	Total reported	134	104	49
	Mean (SD)	43.83 (18.56)	28.66 (20.65)	27.47 (19.13)
	T-Test of change from randomization		<0.001†	<0.001†
Self-image‡	Total reported	134	104	49
	Mean (SD)	42.66 (26.63)	30.69 (29.06)	28.40 (28.56)
	T-Test of change from randomization		0.001†	0.008†
Intercourse‡	Total reported	116	86	38
	Mean (SD)	62.64 (25.10)	41.35 (30.56)	38.29 (30.28)
	T-Test of change from randomization		<0.001†	<0.001†

* A lower mean score indicates greater improvement.
† T-test significance defined as $p \leq 0.05$
‡ Prespecified scale
Abbreviations: ITT = intent-to-treat, SD = standard deviation

Table 9. Study 268. SF-36 mean responses* and test of change from randomisation (ITT population)

SF-36 Scale		DMPA-SC		
		Randomization	Month 6	Month 18
Physical function‡	Total reported	135	103	49
	Mean (SD)	69.61 (21.66)	82.61 (18.84)	81.33 (21.72)
	T-Test of change from randomization		<0.001†	0.001†
Role physical‡	Total reported	135	103	49
	Mean (SD)	31.73 (34.17)	66.02 (41.40)	55.10 (44.77)
	T-Test of change from randomization		<0.001†	0.001†
Bodily pain	Total reported	135	104	49
	Mean (SD)	39.00 (16.34)	61.26 (24.56)	56.18 (23.67)
	T-Test of change from randomization		<0.001†	<0.001†
General health	Total reported	133	104	49
	Mean (SD)	56.05 (21.70)	62.67 (22.64)	64.61 (21.52)
	T-Test of change from randomization		<0.001†	0.016†
Vitality	Total reported	135	104	49
	Mean (SD)	38.11 (18.56)	47.39 (22.24)	50.10 (23.75)
	T-Test of change from randomization		<0.001†	0.007†
Social functioning‡	Total reported	135	104	49
	Mean (SD)	56.94 (22.94)	72.12 (25.49)	70.66 (26.83)
	T-Test of change from randomization		<0.001†	0.038†
Role emotional	Total reported	134	103	49
	Mean (SD)	54.23 (41.62)	67.31 (40.15)	68.03 (40.23)
	T-Test of change from randomization		0.036†	0.149
Mental health	Total reported	135	104	49
	Mean (SD)	62.47 (18.05)	70.27 (17.34)	70.78 (16.58)
	T-Test of change from randomization		0.002†	0.124

* A higher mean score indicates greater improvement.
† T-test significance defined as $p \leq 0.05$
‡ Prespecified scale
Abbreviations: ITT = intent-to-treat, SD = standard deviation

There was one pregnancy in the DMPA-SC group during the treatment period. This 23 year old woman had a positive pregnancy test (with ultrasound confirmation) three months after treatment with an estimated date of conception 72 days post injection. She was withdrawn from the study and had an elective termination.

Efficacy Summary

This was an investigator blinded randomised Phase III trial comparing the efficacy of DMPA-SC to the GnRH agonist leuprolide in women with signs and symptoms of endometriosis. The sample size was smaller than desired (274 instead of 320) with 136 DMPA-SC and 138 leuprolide subjects in the ITT population and 65 and 77 respectively in the Evaluable population (compared to the desired 105 per group).

The primary endpoint was the improvement (of at least one level) in at least 4 of the 5 symptoms/signs after six months of treatment. The "equivalence" or non-inferiority

criteria set between DMPA-SC and leuprolide was a difference of no more than 20% of subjects improving on the 4 symptoms/signs. This criterion was met for dysmenorrhoea, dyspareunia, pelvic pain and pelvic tenderness but not for induration in the ITT population. For the Evaluable population, the non-inferiority criteria were met for dysmenorrhoea, pelvic pain and pelvic tenderness. DMPA-SC was effective at reducing symptoms and signs of endometriosis with a clinically meaningful (more than 4 points), and statistically significant reduction in the composite score of -6.2 (compared to -7.7 for leuprolide). While clinically meaningful reductions were seen in the ITT and Evaluable populations, the response was consistently greater with leuprolide.

Symptom and sign reduction was maintained for the 12 months after treatment cessation across the 5 symptoms/signs (mean composite score change of -5.3 and -5.1) and non-inferior to leuprolide. Significant improvement in QoL was also seen using two assessment tools (EPH-30 and SF-36) at Month 6 and 18. There was one pregnancy in DMPA-SC group with conception estimated to have occurred at about 70 days post injection.

Study 270 – Endometriosis Efficacy

Methods

This was a Phase III randomised, investigator blinded multicentre trial comparing the efficacy and safety of DMPA-SC to leuprolide in the treatment of endometriosis. The study was conducted between 2001 and 2003 at 37 centres in 12 countries (Brazil, Chile, Mexico, Peru, Hungary, Netherland, Poland, Sweden, Italy, Indonesia, Thailand and New Zealand). The design and objectives were the same as in Study 268 and these were assessed using the same endpoints, visit schedule and procedures.

Study treatment was randomised in a 1:1 ratio. DMPA-SC was administered as in Study 268; 104 mg/0.65 mL subcutaneous injection (abdomen or anterior thigh) every 3 months while the administration of leuprolide differed between countries: in the Netherlands 11.25 mg was given by SC injection every 3 months whereas in most other countries it was given as 3.75 mg SC injections every month (except in Peru where it was given as 3.75 mg injection IM each month). Subjects received two doses of DMPA-SC and six doses of leuprolide (except in the Netherlands where two doses were given) during the six month treatment period. All injections were in prefilled syringes. Separate study staff administered the injections to maintain the investigator blinding. Daily calcium tablets were provided.

Study participants

The inclusion and criteria were the same as Study 268, except that hysterectomy was not an exclusion criterion.

Outcomes/endpoints and statistical methods

The efficacy and safety variables were the same as in Study 268.

Sample size: A sample size of 160 subjects per group (105 evaluable per group) was calculated using the same criteria as in Study 268.

Statistical methods: The statistical methods were the same as Study in 268.

Results

Participant flow: There were 319 subjects enrolled, of these one woman was enrolled and not treated and 19 were removed for quality issues (see below). This resulted in 299 subjects in the ITT group, 153 were given DMPA-SC and 146 administered leuprolide. The full six month treatment period was completed by 138/153 (90.2%) and 136/146 (93.2%) women in the DMPA-SC and leuprolide groups, respectively. There were 99/138

(71.7%) and 100/136 (73.5%) subjects in the respective groups who completed the 12 month follow up. Premature discontinuations occurred in 15/153 (9.8%) DMPA-SC and 10/146 (6.8%) leuprolide subjects during the treatment period and this was notably less than in Study 268 (35% and 26% respectively). There were 105 DMPA-SC and 100 leuprolide subjects who met the criteria for the Evaluable group.

There were a variety of protocol deviations including: four DMPA-SC and one leuprolide subject with pain for less than three months prior to enrolment; 30 DMPA-SC and 18 leuprolide subjects who did not meet the endometriosis pain score at either baseline or randomisation (although the total score was at least 6); and 13 DMPA-SC and 9 leuprolide subjects who had baseline BMD T-scores of <1.0. In addition one subject received one SC leuprolide injection IM.

Conduct of study: The study protocol was amended twice. Amendment 1 was issued prior to subject enrolment and revised the washout times, clarified inclusion criteria and leuprolide administration and added a lipid substudy in four European countries. Amendment 2 removed BMD assessments in subjects prematurely discontinuing and removed a further 12 month follow up of subjects at the end of the study. Data quality issues were noted at a site in Indonesia which had included nine DMPA-SC and ten leuprolide subjects. All data from these subjects were removed from the overall analysis.

Baseline data: The groups were similar in terms of age (mean 31 years) and BMI (mean 24 kg/m^2) but there were less White (56.2% versus 64.4%) and more Asian/Pacific Islanders (17.6% versus 5.5%) in the DMPA-SC group. Pre-treatment endometriosis scores were similar between groups on individual items however the composite score was statistically significantly higher in the leuprolide group (9.3 DMPA-SC versus 9.8 leuprolide, p=0.039). There were two women, one in each group, who did not have a baseline composite score of at least 6 (both had scores of 5). Bleeding and medical histories were similar between groups as was prior medication use. During the six month treatment period, 75.2% and 78.8% of the DMPA-SC and leuprolide groups, respectively, took concomitant medications with no apparent differences between groups.

Compliance: Some 93.5% of the DMPA-SC group received both their injections and 93.6% of the leuprolide group received all their scheduled injections. Less than 9% of patients in the DMPA-SC group and less than 15% of patients in the leuprolide group received study medication outside of the protocol-specified window.

Outcomes and estimation

Primary outcome: At 6 months, all 5 signs and symptoms of endometriosis were statistically non-inferior to leuprolide with the lower limit of the 96% CI of the difference in proportion responding (at least one score level) being above -20% (p<0.02) in the ITT population. The difference in effect on induration at 6 months was more pronounced with leuprolide although it just reach statistical non-inferiority (84% versus 95%; 96% CI -19.45, 3.38; p=0.016). At Month 18, after 12 months of follow up, response rates continued to be over 75% and DMPA-SC continued to be non-inferior to leuprolide on 4 of 5 of the symptoms and signs (dysmenorrhoea, pelvic pain, pelvic tenderness and induration), while dyspareunia no longer met the criteria for non-inferiority (96% CI: -22.46, 2.54). In the Evaluable population, results were similar to the ITT population at Month 6, with non-inferiority for all 5 signs/symptoms, and at Month 18 where non-inferiority was noted for all symptoms except dyspareunia (86.4% versus 94.4%, p=0.024) (Table 10). In the analysis of the ITT population with LOCF, the response at Month 6 was non-inferior for the 5 signs/symptoms (Table 11).

Table 10. Study 270. Signs and symptoms of endometriosis: response* in individual components at 6, 12 and 18 months (evaluable population).

Component Visit	DMPA-SC		Leuprolide		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea						
Month 6 (EOT)	103	94 (91.3)	99	97 (98.0)	<0.001§	-13.13, -0.30
Month 12	88	76 (86.4)	89	71 (79.8)	<0.001§	-4.95, 18.12
Month 18	69	59 (85.5)	76	62 (81.6)	<0.001§	-8.70, 16.55
Dyspareunia						
Month 6 (EOT)	71	58 (81.7)	70	62 (88.6)	0.014§	-19.13, 5.37
Month 12	58	50 (86.2)	64	55 (85.9)	<0.001§	-12.63, 13.17
Month 18	44	38 (86.4)	54	51 (94.4)	0.024	-20.49, 4.33
Pelvic Pain						
Month 6 (EOT)	105	87 (82.9)	100	91 (91.0)	0.005§	-17.72, 1.43
Month 12	89	78 (87.6)	88	73 (83.0)	<0.001§	-6.23, 15.61
Month 18	71	61 (85.9)	77	61 (79.2)	<0.001§	-6.04, 19.43
Pelvic Tenderness						
Month 6 (EOT)	101	81 (80.2)	92	78 (84.8)	0.002§	-15.79, 6.62
Month 12	85	66 (77.6)	81	63 (77.8)	0.001§	-13.41, 13.15
Month 18	66	53 (80.3)	71	60 (84.5)	0.008§	-17.59, 9.18
Induration						
Month 6 (EOT)	93	67 (72.0)	87	68 (78.2)	0.015§	-19.32, 7.09
Month 12	76	62 (81.6)	79	63 (79.7)	<0.001§	-11.20, 14.86
Month 18	59	49 (83.1)	67	52 (77.6)	<0.001§	-9.06, 19.94

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment.
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
Abbreviations: CI = confidence interval, EOT = end of treatment

Table 11. Study 270. Signs and symptoms of endometriosis: response* in individual components at 6 months (ITT population LOCF analysis).

Component	DMPA-SC N = 153		Leuprolide N = 146		P-Value‡	96% CI
	Total Reported	n (%)†	Total Reported	n (%)†		
Dysmenorrhea	151	134 (88.7)	145	138 (95.2)	<0.001§	-12.86, 0.00
Dyspareunia	101	82 (81.2)	95	79 (83.2)	<0.001§	-13.20, 9.26
Pelvic pain	152	122 (80.3)	146	129 (88.4)	0.002§	-16.68, 0.50
Pelvic tenderness	148	116 (78.4)	140	113 (80.7)	<0.001§	-12.10, 7.43
Induration	128	90 (70.3)	127	98 (77.2)	0.008§	-18.14, 4.44

* Response (ie, improvement) defined as a decrease of at least 1 point in the score relative to pretreatment (primary endpoint was the response at month 6)
† % = (n/total reported within period) x 100
‡ The p-value tests the null hypothesis DMPA-SC % improved - leuprolide % improved ≤-20%. Treatment equivalence was concluded when p<0.02.
§ Statistically equivalent between treatment groups (p<0.02).
Abbreviations: CI = confidence interval, ITT = intent-to-treat, LOCF = last observation carried forward

At Month 6 (ITT population), the mean change in the endometriosis signs/symptoms composite score was -6.3 for the DMPA-SC group and -7.3 for the leuprolide group. The reduction in symptoms from baseline to Month 6 was statistically significant for both treatment groups ($p<0.001$), although there was a significantly greater effect with leuprolide (95% CI for the difference 0.2, 1.9). At Month 18, there remained a clinically meaningful reduction in both groups (-6.6 versus -6.1) and the added benefit of leuprolide was no longer evident (95% CI: -1.7, 0.7). Similar results were also found for the Evaluable population and supported at Month 6 by analysis of the ITT population with LOCF, composite score reduction (-6.0 versus -6.9, 95% CI: 0.1, 1.8).

Excluding dyspareunia from the composite score analysis did not change the results. At Month 6 in the ITT population the composite score reduction was -5.0 for DMPA-SC and -6.0 for leuprolide (95% CI: 0.5, 1.6) with the treatment no longer in favour of leuprolide at Month 18 (-5.0 DMPA-SC versus -4.8 leuprolide, 95% CI: -1.0, 0.6). Similar results were seen for the Evaluable population.

Subgroup analysis for BMI category (≤25, 25-≤30, >30 kg/m^2), race (White, Black, Asian/Pacific Islander, mixed/multiracial), and age (<25, 25-≤35, >35 years) did not reveal any major differences between groups. It is noted that there were only nine Black women in the study.

Secondary Outcomes: The mean change in each symptom and sign from baseline to Month 6 shows a reduction in all symptoms/signs but with the greatest effect on dysmenorrhoea (-1.7 DMPA-SC versus -2.2 leuprolide). For women completing the 6 months of treatment, the median time to worsening of symptoms during the 12 month follow up period was longer for dysmenorrhoea (184 versus 92 days) and pelvic pain (227 versus 120 days) in the DMPA-SC group. The time to worsening of dyspareunia and induration was similar in both groups.

As measured by the EHP-30, subjects reported an improvement in QoL (lower score) in both treatment groups at Month 6 and through to Month 18. An improvement in QoL was also seen with the SF-36.

There were no pregnancies during the six month treatment period in either group. During the 12 months of follow up there was 6/138 (4.3%) DMPA-SC subjects and 9/136 (6.6%) leuprolide subjects who became pregnant. One pregnancy also occurred in the leuprolide group during follow up at the Indonesian site and the data for this woman were excluded.

Efficacy Summary

This study had the same design as Study 268 with the only main difference being that the administration of leuprolide was by monthly SC injection for the majority of women. There were 299 women in the ITT population and the study just met the sample size requirement with 105 DMPA-SC and 100 leuprolide subjects in the evaluable group (the aim was 105 per group). Women had similar baseline endometriosis pain scores as In Study 268 (approximately 10).

Treatment with DMPA-SC met the non-inferiority criteria at Month 6 on all 5 of the endometriosis signs/symptoms. Results were consistent across analysis populations including the ITT LOCF analysis which would be more conservative as it includes subjects withdrawn before Month 6 who may have higher scores due to being treated for a shorter time. The composite score showed a clinically meaningful reduction for both treatment groups at Month 6 (-6.3 DMPA-SC and -7.3 leuprolide) which continued after treatment cessation until Month 18 (-6.6 versus -6.1). The results showed a greater effect with leuprolide at Month 6 (95% CI: 0.2, 1.9) but this difference in effect was no longer significant at Month 18. Both treatments showed improvements in QoL as measured by

the EHP-30 and the SP-36 at Month 6 which were maintained 12 months after treatment cessation.

Clinical studies in special populations

There were no studies in special populations included in the current Australian submission. Age, BMI and race did not affect the contraceptive efficacy of DMPA-SC nor its efficacy in the treatment of endometriosis, although there were only small numbers of Black women included in the endometriosis studies.

Analysis performed across trials (pooled analysis and meta-analysis)

There were no pooled analyses or meta-analyses included in the current Australian submission.

Evaluators overall conclusions on clinical efficacy

Contraception

The dose finding Study 265 assessed four SC doses, 50 mg, 75 mg 100 mg and 150 mg of the IM formulation with the endpoint being suppression of ovulation as measured by serum progesterone. This found 100 mg to be the most effective dose as it suppressed ovulation in all women when one woman's results were removed (outlier; presumed injection near or into a blood vessel) and also maintained the MPA concentration above the threshold level of 0.20 ng/mL at Day 91. For practical reasons of syringe volume the dose for the subcutaneous formulation was set at 104 mg/0.65 mL and this formulation was used in all other clinical studies.

There were three Phase III trials assessing the contraceptive efficacy of DMPA-SC, two were open label, non-comparative, one year trials (Study 267 and 269) and one was a randomised two year trial with DMPA-IM as the comparator (Study 267BMD). They included healthy women, 18 to 49 years old (18 to 35 years old in Study 267BMD), in North and South America, Europe and Asia. The exclusion criteria were as would be expected for hormonal contraceptives. In all studies the dose of DMPA-SC was 104 mg/0.65 mL given subcutaneously to the abdomen or anterior thigh. The primary efficacy endpoint was treatment failure cumulative pregnancy rate. The pregnancy rate was calculated using life table methods and Pearl Index. Pregnancy testing was by urinary pregnancy test kits and conducted every 91 days.

These trials included data from a total of 2045 women receiving DMPA-SC with a total of 23,025 cycles of exposure and 19,588 cycles of exposure with risk of pregnancy (excluding months when barrier contraception was used sometimes or no intercourse occurred). The mean age was 30.0 years, with 82.4% White, 4.9% Black, 2.5% Asian/Pacific Islander and 10.2% of mixed background or multiracial. BMI distribution was 64.5%, 22.7% and 12.6% for ≤25, >25 to ≤30 and >30 kg/m^2, respectively.

DMPA-SC was an effective contraceptive as there were no pregnancies reported in any of the three trials, with a treatment failure cumulative pregnancy rate of 0% and a Pearl Index of 0.0 pregnancies per 100 woman years.

There were three pregnancies reported in other trials. In the Phase I/II Study 272, there was a pregnancy in a woman with conception 190 days after a single dose of DMPA-SC. In the Phase III endometriosis trial Study 268, there was one pregnancy in a 23 year woman with an estimated conception date 72 days after her first injection of DMPA-SC. In the Phase III Study 267, there was one undetected pregnancy (negative urine pregnancy test) at study entry with a spontaneous abortion three weeks after the first dose. For DMPA-IM, there was one pregnancy in Study 267BMD with a Pearl Index of 0.28 pregnancies per 100 women years (95% CI: 0.0, 0.83).

The small number of Asian or Black women in the Phase III program limited the ability to draw any definitive conclusions about treatment in these populations. However PK/PD studies indicated no concerning differences. Postpartum women and adolescents were not specifically studied so any conclusions on these populations cannot be made. A number of the women in the Phase III program self injected (either at home or at the study site) and this amounted to 6279 women cycles of exposure with no reported pregnancies.

Data from the PK/PD Study 272 showed that the earliest return to ovulation was 15 weeks after a single dose of DMPA-SC. Data from the substudy of Study 267 was not provided for review although it was reported that 12 of 15 women had serum progesterone evidence of ovulation within one year after treatment cessation.

Endometriosis

The efficacy of DMPA-SC was assessed in two investigator blinded randomised Phase III trials comparing the efficacy of DMPA-SC to the GnRH agonist leuprolide in 573 women with signs and symptoms of endometriosis (Studies 268 and 270). Subjects were treated for six months and followed up for a further 12 months after treatment cessation. Five signs/symptoms of endometriosis pain (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration) were assessed on a score from 0 to 3. The studies included otherwise healthy women aged 18 to 49 years with laparoscopy diagnosed endometriosis and a total symptom score of at least 6 with a score of at least two on dysmenorrhoea, dyspareunia and pelvic pain.

The primary endpoint was the improvement (of at least one level) in at least 4 of the 5 symptoms/signs after 6 months of treatment. The “equivalence” or non-inferiority criteria set between DMPA-SC and leuprolide was a difference in proportion of subjects improving on the 4 items of no more than -20%. While the primary endpoint was based on a responder analysis, a composite score was also calculated with a reduction of 4 being classed as clinically meaningful.

The two studies included 573 women. In Study 268, there were 136 DMPA-SC and 138 leuprolide subjects and 65 and 77, respectively, were evaluable. This was a smaller sample size than the desired 105 per group. Study 270 included 299 women in the ITT population and the study just met the sample size requirement with 105 DMPA-SC and 100 leuprolide subjects in the Evaluable group. The average age of women in the studies was 26 and 31 years, respectively, with similar baseline endometriosis pain scores of approximately 10 points.

In Study 268, the non-inferiority criteria were met at Month 6 for dysmenorrhoea, dyspareunia, pelvic pain and pelvic tenderness but not for induration in the ITT population. For the Evaluable population, the non-inferiority criteria were met for dysmenorrhoea, pelvic pain and pelvic tenderness. In Study 270 the non-inferiority criteria were met for all 5 of the endometriosis signs/symptoms. Results were consistent across analysis populations including the ITT LOCF analysis which would be more conservative as it includes subjects withdrawn before Month 6 who may have higher scores as they had been treated for a shorter time.

In Study 268, a clinically meaningful, statistically significant reduction in the composite score at Month 6 of -6.2 (compared to -7.7 for leuprolide) was found in the ITT population. Similar results were found In Study 270 with a composite score reduction at Month 6 of -6.3 (compared to -7.3 for leuprolide). The Evaluable population results showed similar composite score results for both studies.

While DMPA-SC met the non-inferiority criteria on the responder rates and resulted in clinically meaningful reduction in the symptoms and signs of endometriosis, the response

to treatment was significantly greater with leuprolide (95% CI for the difference in composite score at Month 6 for Study 268 was 0.5 to 2.6 and for Study 270 it was 0.2 to 1.9).

In both studies, reduction in symptoms and signs was maintained across the 5 items for the 12 months after DMPA-SC treatment ceased and DMPA-SC was non-inferior to leuprolide. The composite score also continued to be reduced with mean changes of -5.3 (Study 268) and -6.6 (Study 270) in the DMPA-SC group at 18 months. At 18 months, there was no longer a significant difference in scores between the two treatments. Significant improvement in QoL was also seen using two assessment tools (EPH-30 and SF-36) at Month 6 and also continued through to Month 18 in both studies.

It was noted that the dropout rate was higher and the Evaluable population smaller in Study 268. However, the clinical evaluator believed the results were still robust due to the strength of the findings, the consistency across the two studies and the consistency within the population groups analysed.

Safety

Introduction

The primary safety data was pooled from the three Phase III contraceptive efficacy trials (Studies 267, 269 and 267BMD) for women receiving DMPA-SC. Supportive safety data comes from the three Phase I/II pharmacology studies (Studies 265, 271 and 272) and the two Phase III endometriosis trials (Studies 268 and 270).

Safety was assessed in the Phase II and III trials by recording adverse events (AE), laboratory evaluations (blood chemistry, haematology and urinalysis), blood pressure and body weight. In addition, specific safety assessments relevant to steroid contraceptives were conducted. These included: BMD (Studies 267BMD, 268 and 270); hormone profiles; bleeding patterns; lipid profile (non fasting In Study 267, 267BMD and 268, fasting in 270); coagulation profile (267, 267BMD, platelet count In Study 268, full profile in 270); and endometrial biopsies (Study 269). Specific analysis of AEs associated with psychiatric disorders, reproductive system, breast disorders and injection site disorders was also undertaken.

Patient exposure

Women who received at least one dose of study medication were included in the safety analysis; a total of 2053 women received DMPA-SC and 268 received DMPA-IM in the contraceptive efficacy studies. The total number of subjects reported was 2043 as ten women who received DMPA-SC did not have AE data available. There were 1388 (67.6%) women who received four injections and a further 158 (7.7%) who received five or more DMPA-SC injections. The mean age of subjects was 30.0 years with 82.4% being White and a mean BMI of 24.3 kg/m^2. Seventy percent of women completed the three trials with the most common reasons for withdrawal being AEs (9.8%), consent withdrawn (12.1%) or lost to follow up (6.6%).

Adverse Events

All subjects treated with DMPA-SC

Adverse events were reported in 59.5% (1216/2043) of women who received DMPA-SC (Table 12). AE reporting was higher in the study conducted in the Americas (70.7%) compared to the studies in Europe and Asia (46.5%). The AE rate In Study 267BMD was 81.4% and the higher rate is likely due to the two year duration.

The most frequent AEs (≥5% of subjects) were headache (8.5%), increased weight (6.9%), intermenstrual bleeding (7.1%) and amenorrhoea (6.4%). Drug related AEs were reported in 39.4% of women, the most frequent being intermenstrual bleeding (7.0%), increased weight (6.7%), amenorrhoea (6.3%), vaginal haemorrhage (3.6%), headache (3.9%) and acne (3.0%) (Table 13). The frequency of drug related AEs was similar between racial groups, 30.8% (16/52) in Asians/Pacific Islanders, 42.0% (42/100) in Blacks and 39.5% (665/1683) in Whites.

Table 12. Summary of subject reporting treatment emergent AEs (ITT population)

	All DMPA-SC N = 2053		267BMD			
			DMPA-SC N = 266*		DMPA-IM N = 268	
	n	%	n	%	n	%
Total subjects reported†	2043	100	263	100	266	100
Adverse events	1216	59.5	214	81.4	207	77.8
Serious adverse events	34	1.7	10	3.8	6	2.3
Drug-related adverse events	805	39.4	144	54.8	149	56
Adverse events leading to discontinuation	203	9.9	47	17.9	59	22.2
Deaths	1	<0.1	0	0	0	0

* These subjects are included in the all DMPA-SC column.
Note that data were unavailable for 10 subjects of the total treated with DMPA-SC (5 from 269, 2 form 267 and 3 from 267BMD) and for 2 subjects treated with DMPA-IM.
Percentages are based on the total subjects reported.
Abbreviations: ITT = intent-to-treat

Table 13. Drug related adverse events reported in ≥1% of subjects (ITT population)

System/Organ Class‡ Preferred Term	All DMPA-SC N = 2053		267BMD			
			DMPA-SC† N = 266		DMPA-IM N = 268	
	n	%	n	%	n	%
Total subjects reported	2043	100	263	100	266	100
Subjects with at least 1 drug-related adverse event	805	39.4	144	54.8	149	56
General disorders and administration site conditions						
Fatigue	30	1.5	4	1.5	2	0.8
Injection site atrophy	23	1.1	7	2.7	0	0
Injection site pain	26	1.3	4	1.5	0	0
Investigations						
Weight increased	136	6.7	32	12.2	38	14.3
Nervous system disorders						
Headache NOS	79	3.9	9	3.4	14	5.3
Psychiatric disorders						
Depression NOS	28	1.4	9	3.4	5	1.9
Irritability	21	1	6	2.3	3	1.1
Libido decreased	54	2.6	8	3	16	6
Reproductive system and breast disorders						
Amenorrhea NOS	129	6.3	2	0.8	5	1.9
Intermenstrual bleeding	143	7	15	5.7	15	5.6
Menometrorrhagia	48	2.3	9	3.4	10	3.8
Menorrhagia	32	1.6	0	0	3	1.1
Menstruation irregular	25	1.2	0	0	3	1.1
Vaginal hemorrhage	74	3.6	6	2.3	5	1.9
Skin and subcutaneous tissue disorders						
Acne NOS	61	3	18	6.8	17	6.4

* The 1% cut-point was based on all DMPA-SC-treated subjects. Both treatment groups in Study 267BMD are included as a comparison.
† These subjects are included in the all DMPA-SC column.
‡ MedDRA version 2.3
Note that data were not available for 10 subjects in the DMPA-SC group (5 from 269, 2 form 267 and 3 from 267BMD) and for 2 subjects in the DMPA-IM group.
Abbreviations: ITT = intent-to-treat, NEC = not elsewhere classified, NOS = not otherwise specified

Depression was reported in 3.2% (65/2043) of women and resulted in discontinuation in 0.8%. Mood disorder was reported as an AE in 1.5% and a reason for discontinuation in 0.4% of subjects. There was also one case each of bipolar disorder, seasonal affective disorder, anger and two suicide attempts.

There were 32.3% of subjects with a reproductive system or breast disorder AE, five of which were SAEs (three uterine haemorrhages, one metrorrhagia and one uterine polyp). The most frequent AEs in this group were bleeding irregularities (intermenstrual bleeding 7.1%, amenorrhea 6.4%, vaginal haemorrhage 3.6% and menometrorrhagia 2.5%). Pap tests were performed at screening (if not done in the previous 12 months) and at 12 months. There were no malignancies reported and one case of cervical intraepithelial neoplasia (CIN) Grade III. Breast pain/tenderness was reported in 2.3% of women. Mammograms were performed in women >35 years at baseline (if not done within 12 months) and at Month 12. There was one breast cancer detected at baseline and one invasive ductal carcinoma diagnosed at Month 11 in a 32 year old woman.

Injection site reactions were reported in 6.1% of women with 0.5% withdrawing due to this AE. The site reactions were nodule/lump (1.9%) atrophy/dimpling (1.5%), pain/tenderness (1.4%) and general (1.4%).

DMPA-SC compared to DMPA-IM

In Study 267BMD adverse event reporting rates were similar between the DMPA-SC and DMPA-IM treated subjects (81.4% versus 77.8%). The rates were similar for increased weight, headache, intermenstrual bleeding and acne but were higher in the DMPA-SC group for injection site reaction (combined terms) (8.0% versus 0.4%), urinary tract infection (7.6% versus 2.3%) and dysmenorrhoea (4.2% versus 1.5%).

DMPA-SC compared to leuprolide

In Study 270, the percentage of patients who had at least one treatment emergent AE (TEAE) was similar in the DMPA-SC (69.7%, 106/152) and leuprolide groups (65.0%, 93/143). There was a significantly higher incidence of intermenstrual bleeding (13.2% versus 1.4%), uterine haemorrhage (4.6% versus 0.7%), and vaginal haemorrhage (4.6% versus 0%) following DMPA-SC treatment and a significantly higher incidence of hot flushes (5.9% versus 17.5%), myalgia (1.3% versus 5.6%) and vaginal discharge (0.7 versus 4.2%) following leuprolide treatment (Table 14).

In Study 268, incidence of TEAEs was again similar between groups, 86.9% (113/130) in the DMPA-SC and 85.2% (115/135) in the leuprolide group. There was a significantly higher percentage of injection site reactions (6.9% versus 0%), "allergies"[17] (5.4% versus 0%) and pelvic pain (6.2% versus 1.5%) with DMPA-SC. The leuprolide group had significantly more hot flushes (2.3% versus 11.9%) and toothache (0% versus 3.7%).

[17] This includes seven seasonal allergies and one allergic reaction to latex.

Table 14. Study 270. TEAEs reported by ≥1% of patients in either group (ITT population)

System/Organ Class* Preferred Term	DMPA-SC n (%)†	Leuprolide n (%)†
Influenza-like illness	3 (2.0)	0
Pyrexia	3 (2.0)	0
Immune System Disorders		
Hypersensitivity NOS	1 (0.7)	3 (2.1)
Infections and Infestations		
Bronchitis NOS	3 (2.0)	5 (3.5)
Cystitis NOS	3 (2.0)	2 (1.4)
Gastroenteritis NOS	1 (0.7)	2 (1.4)
Infection NOS	2 (1.3)	1 (0.7)
Influenza	7 (4.6)	4 (2.8)
Nasopharyngitis	6 (3.9)	7 (4.9)
Otitis media NOS	0	2 (1.4)
Pharyngitis NOS	4 (2.6)	3 (2.1)
Pneumonia NOS	0	2 (1.4)
Sinusitis NOS	1 (0.7)	3 (2.1)
Upper respiratory tract infection NOS	3 (2.0)	0
Urinary tract infection NOS	3 (2.0)	3 (2.1)
Vaginitis	6 (3.9)	7 (4.9)
Injury and Poisoning		
Road traffic accident	0	2 (1.4)
Investigations		
Weight decreased	1 (0.7)	2 (1.4)
Weight increased	3 (2.0)	4 (2.8)
Musculoskeletal, Connective Tissue, and Bone Disorders		
Arthralgia	7 (4.6)	7 (4.9)
Back pain	11 (7.2)	7 (4.9)
Muscle cramps	3 (2.0)	1 (0.7)
Myalgia	2 (1.3)	8 (5.6)‡
Neck pain	2 (1.3)	0
Pain in limb	3 (2.0)	3 (2.1)
Polyarthralgia	1 (0.7)	3 (2.1)
Nervous System Disorders		
Dizziness (excluding vertigo)	2 (1.3)	6 (4.2)
Formication	3 (2.0)	0
Headache NOS	13 (8.6)	18 (12.6)
Headache NOS aggravated	2 (1.3)	1 (0.7)
Hypersomnia	7 (4.6)	3 (2.1)
Insomnia NEC	2 (1.3)	7 (4.9)
Paresthesia NEC	2 (1.3)	4 (2.8)
Syncope	2 (1.3)	0
Psychiatric Disorders		
Anorgasmia	0	2 (1.4)
Anxiety NEC	4 (2.6)	1 (0.7)
Depression NEC	6 (3.9)	6 (4.2)

Table 14 continued. Study 270. TEAEs reported by ≥1% of patients in either group (ITT population)

System/Organ Class* Preferred Term	DMPA-SC n (%)†	Leuprolide n (%)†
Irritability	3 (2.0)	1 (0.7)
Libido decreased	6 (3.9)	7 (4.9)
Loss of libido	1 (0.7)	2 (1.4)
Renal and Urinary Disorders		
Dysuria	3 (2.0)	1 (0.7)
Reproductive System and Breast Disorders		
Breast disorder NOS	2 (1.3)	0
Breast engorgement	2 (1.3)	1 (0.7)
Breast pain	8 (5.3)	5 (3.5)
Breast tenderness	4 (2.6)	0
Dyspareunia NEC	0	2 (1.4)
Endometriosis	2 (1.3)	0
Galactorrhea	1 (0.7)	3 (2.1)
Intermenstrual bleeding	20 (13.2)‡	2 (1.4)
Menorrhagia	2 (1.3)	1 (0.7)
Menstruation irregular	2 (1.3)	0
Uterine hemorrhage	7 (4.6)‡	1 (0.7)
Vaginal discharge	1 (0.7)	6 (4.2)‡
Vaginal hemorrhage	7 (4.6)‡	0
Vulvovaginal dryness	2 (1.3)	5 (3.5)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea NOS	2 (1.3)	2 (1.4)
Rhinitis allergic NOS	0	2 (1.4)
Rhinitis seasonal	2 (1.3)	0
Skin and Subcutaneous Tissue Disorders		
Acne NOS	3 (2.0)	2 (1.4)
Alopecia	2 (1.3)	4 (2.8)
Dermatitis acneiform	2 (1.3)	0
Ecchymosis	0	2 (1.4)
Genital pruritus NOS	2 (1.3)	1 (0.7)
Pruritus NOS	2 (1.3)	1 (0.7)
Skin odor abnormal	1 (0.7)	2 (1.4)
Urticaria NOS	2 (1.3)	0
Vascular Disorders		
Hot flushes NOS	9 (5.9)	25 (17.5)‡

* MedDRA version 2.3
† % = (n/total reported) x 100
‡ Significantly different between treatment groups, Chi-square test; significance defined at p≤0.05.
Abbreviations: ITT = intent-to-treat, NEC = not elsewhere classified, NOS = not otherwise specified

Bleeding patterns

Bleeding pattern was assessed through daily subject completed diaries in the three contraceptive efficacy trials. Bleeding was categorised over a 30 day period as: no bleeding and/or spotting; spotting only; bleeding only; and bleeding and spotting. The days were grouped as: 0, 1-7, 8-10 and 11-30 days. Regular menstruation in the three months prior to enrolment was a study inclusion criterion. Amenorrhoea (no bleeding or spotting) increased with treatment duration from 26.5% at Month 3 to 56.5% at Month 12 (Figure 5). The proportion of women with spotting only, bleeding and spotting or bleeding only is presented in Figure 6. The proportion of women bleeding and/or spotting for 11-30 days

per month reduced from 36.4% at Month 3 to 28.1% at Month 6 and 14.3% at Month 12. The incidence of amenorrhoea at one year did not change with BMI: 54.4% for subjects with BMI ≤25; 60.7% subjects with BMI >25 to ≤30; and 60.1% for subjects with BMI >30 kg/m^2.

Figure 5. Percent of DMPA-SC treated women with amenorrhea per 30-day month (ITT population, N=2053).

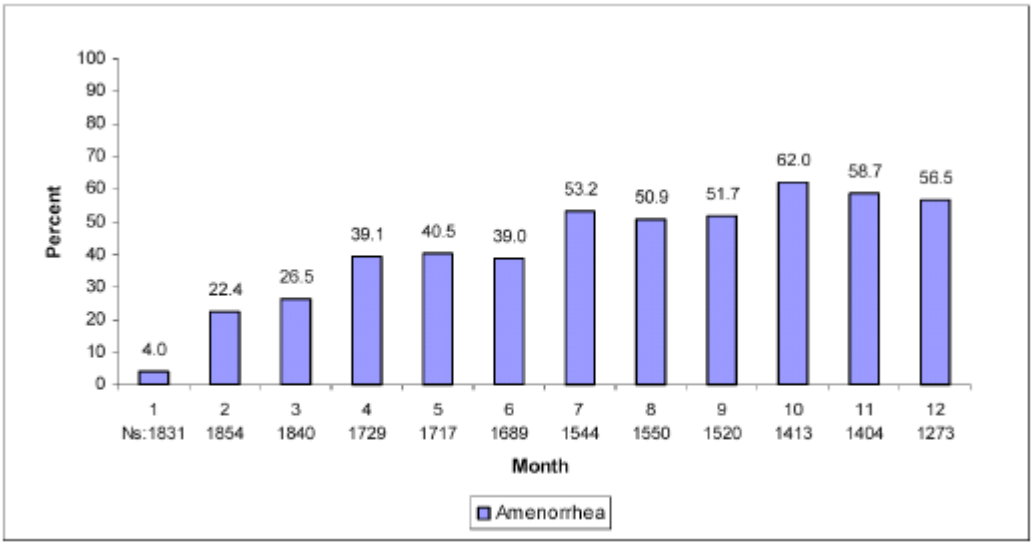
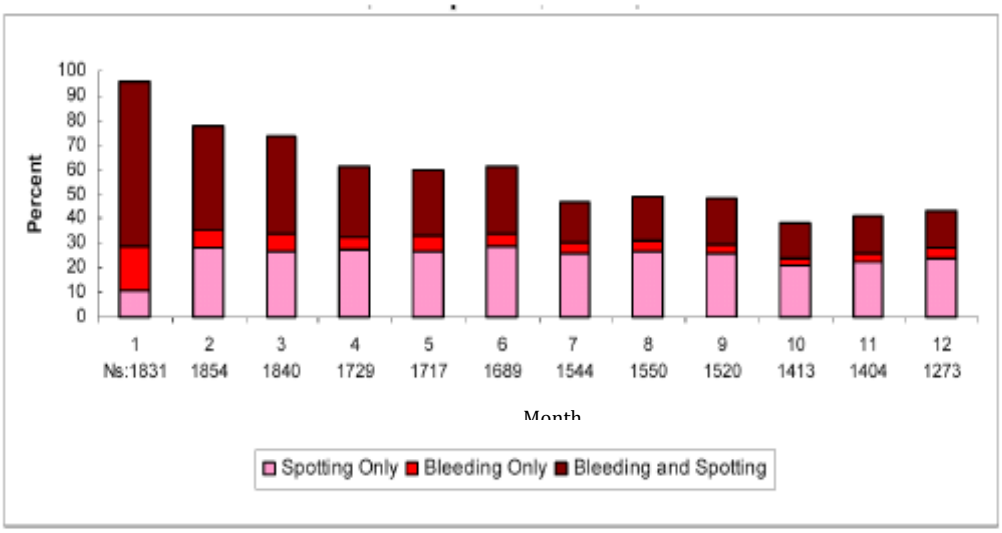


Figure 6. Percent of DMPA-SC treated women with bleeding and/or spotting per 30-day month (ITT population, N=2053).



Bone mineral density

The change in BMD was assessed In Study 267BMD at 12, 24 and 36 months and in the endometriosis Studies 268 and 270 at 6, 12 and 18 months. Data were available from 106 DMPA-SC and 101 DMPA-IM subjects at Month 24 in Study 267BMD, and 289 subjects in Studies 268 and 270. Measurements were taken at the lumbar spine and proximal femur using DXA scanners. Due to variation in reproducibility of results (0.5% for spine and 1.0-2.0% for hip) a change of 2.0% was deemed necessary to define true bone loss between periods.

After 24 months of treatment in Study 267BMD the median percentage change in BMD of the spine was -4.3% and -5.0%, and for the hip was -3.3% and -3.6%, for the DMPA-SC and DMPA-IM groups, respectively. By Month 36, the median change was -5.4% and -4.6% for the spine and -5.5% and -5.2% for the hip in the two groups, respectively. These results were not significantly different from the baseline value. The only statistically significant difference between treatment groups was at Month 12 in the spine (-2.4% DMPA-SC group versus -3.4% DMPA-IM group) (p=0.021). After 6 months of treatment in the endometriosis studies, the median change in hip BMD was -0.4% for the hip and -1.0% for the spine. By 18 months there was some improvement with the median change being -0.2% for the hip and -0.25% for the spine. Race or geographical location did not appear to affect the results. There was a trend for a greater loss in the BMD of the hip with increasing BMI in Study BMD267.

There were slightly more subjects with a loss of ≥5% in hip and spine BMD in the DMPA-IM group compared to the SC group. Such a loss from the spine BMD was found in 20.5% (34/166) of DMPA-SC subjects and 24.7% (40/162) of DMPA-IM subjects after one year and 37.7% (40/106) of DMPA-SC subjects and 51.0% (52/102) of DMPA-IM after two years. For the hip, a loss of ≥5% was found in 28.3% (30/106) of DMPA-SC subjects and 33.7% (34/101) of DMPA-IM subjects at two years.

Subjects were assessed for change in T-score category (-1.49 to -1.00, -0.99 to -0.50, -0.49 to 0.00, 0.01 to 0.50, 0.51 to 1.00, 1.01 to 1.50, and >1.50). For subjects treated with DMPA-SC there was an increasing shift to a lower T-score category with time; for the spine BMD, 47.6% of subjects had shifted to a lower category by 12 months and 74.2% had shifted by 3 years. There were 12.3% (13/106) of DMPA-SC and 11.8% (12/102) of DMPA-IM subjects who had a spine T-score < -1.0 at Month 24 (that is, meeting the definition of osteopenia). No subjects had a T-score of less than -2.5. In Studies 268/270, a spine T-score of -1.0 or lower was present in 3.9% at baseline and 10.0% at Month 6. There were six reported fractures In Study 267BMD but none were considered osteoporotic in nature.

DMPA-SC compared to leuprolide

In Studies 268 and 270, the primary safety endpoint was the median percentage change in BMD after 6 months of treatment relative to baseline. In Study 268, there was a significantly smaller decline in BMD in the DMPA-SC group compared to the leuprolide group for both femur (-0.30% versus -1.65%; p<0.001) and lumbar spine (-1.10% versus -3.95%; p<0.001). At Month 18, 12 months after cessation of study medication, spine BMD had recovered and was close to baseline in the DMPA-SC group. While improved, it was still reduced from baseline in the leuprolide group (median change 0.2% versus -1.7%, p=0.021) At Month 6, there was a corresponding lower proportion of osteopenic subjects (T-score <1.0) in the DMPA-SC group, 1.3% versus 14.3% for femur and 5.2% versus 15.3% for spine (Table 15).

Table 15. Study 268. Femur and lumbar spine total BMD T-scores <-1.0 (ITT population)

Visit	T-Score Femur Total (Less Than -1)		T-Score Spine Total (Less Than -1)	
	DMPA-SC n/N (%)	Leuprolide n/N (%)	DMPA-SC n/N (%)	Leuprolide n/N (%)
Baseline	2/131 (1.5)	7/138 (5.1)	5/132 (3.8)	5/138 (3.6)
Month 6 (EOT)	1/77 (1.3)	14/98 (14.3)	4/77 (5.2)	15/98 (15.3)
Month 12	1/50 (2.0)	6/64 (9.4)	2/51 (3.9)	6/63 (9.5)
Month 18	1/32 (3.1)	4/42 (9.5)	3/31 (9.7)	2/42 (4.8)

Abbreviations: BMD = bone mineral density, EOT = end of treatment, ITT = intent-to-treat

In Study 270, the results were similar to Study 268 with a significantly smaller decrease in BMD of both the spine (-1.0% versus -4.0%, p<0.001) and femur (-0.5% versus -2.1%, p<0.001) in subjects treated with DMPA-SC compared to leuprolide. The difference was significant at 12 months for spine and femur but was no longer significant at 18 months for the spine BMD (-0.4% versus -1.3%, p=0.08). The lower risk of osteopenia with DMPA-SC at Month 6 was only noted in the spine BMD (12.7% versus 21.2%) (Table 16). There were no notable differences in the subgroup analysis by age, BMI or race in either study.

Table 16. Study 270. Femur and lumbar spine total BMD T-scores <-1.0 (ITT population)

Visit	T-Score Femur Total (Less Than -1.0)				T-Score Spine Total (Less Than -1.0)			
	DMPA-SC		Leuprolide		DMPA-SC		Leuprolide	
	Total Reported	n (%)*	Total Reported	n (%)*	Total Reported	n (%)*	Total Reported	n (%)*
Baseline	149	12 (8.1)†	143	6 (4.2)	148	6 (4.1)	145	6 (4.1)†
Month 6 (EOT)	131	10 (7.6)	130	5 (3.8)	134	17 (12.7)	132	28 (21.2)
Month 12	119	8 (6.7)	118	6 (5.1)	119	12 (10.1)	118	22 (18.6)†
Month 18	93	10 (10.8)	93	2 (2.2)	93	8 (8.6)	91	12 (13.2) ††

* % = (n/total reported within period) x 100
† Includes 1 patient with a T-score of -1.
†† Includes 2 patients with a T-score of –1.
Abbreviations: EOT = end of treatment, ITT = intent-to-treat, BMD = bone mineral density

Endometrial biopsy, hormone profile and hypoestrogenic symptoms

Endometrial biopsies were conducted at baseline and Month 12 in a subgroup of Russian subjects in Study 269. At baseline, 0.6% (1/164) of subjects had an atrophic endometrium which had increased by Month 12 to 30.9% (34/110) with a further 47.3% (52/110) having insufficient biopsy samples for diagnosis. The corresponding median endometrial thickness was 7.6 mm at baseline and 4.0 mm at Month 12.

Levels of estradiol, progesterone and sex hormone binding globulin (SHBG) were analysed in Study 269 and 267BMD at enrolment (first 5 days of the menstrual cycle) and in Month 6, 12 and 24. These all showed a decrease in median levels over this time but due to inter-subject variability no definitive conclusions could be drawn.

Study 268 and 270 assessed hypoestrogenic symptoms using the Kupperman Index[18] at baseline and then monthly until Month 6. In Study 268 at Month 6, the median change in Kupperman Index was -2.0 for DMPA-SC and +1.0 for leuprolide (p=0.002) and in Study 270 the same parameter was 0.0 for the DMPA-SC group and +6.0 for the leuprolide group (p<0.001). This indicates that leuprolide results in fewer oestrogen related symptoms. Hot flushes were recorded on the daily diary. At Month 6 the median average daily number of hot flushes was 0.0 for DMPA-SC and 1.9 for leuprolide in Study 268 and 0.0 for DMPA-SC and 2.0 for leuprolide in Study 270 (p<0.001 both studies). In the two studies, the rate of severe hot flushes from baseline to Month 6 remained similar for the DMPA-SC group (16.7% and 11.0% at baseline to 7.6% and 8.9% at Month 6) but increased in the leuprolide group (24.6% and 14.1% at baseline to 35.2% and 47.4% at Month 6).

Serious Adverse Events and Deaths

Deaths

There was one death (<0.1%) reported which was not likely to be related to study medication.

SAEs

In the 2053 subjects treated with DMPA-SC, there were 36 (1.8%) serious adverse events (SAEs) (Table 17). The frequency was similar across studies: 1.3% (9/720) in Study 267; 1.4% (15/1060) in Study 269; and 3.8% (10/263) in Study 267BMD. SAE rates were similar between DMPA-SC and DMPA-IM in Study 267BMD (3.8% versus 2.3%). For women treated with DMPA-SC, there were three cases of abdominal pain, three of uterine haemorrhage and two cases each of depression and suicide attempt. There was also one incidence of breast cancer, one breast fibroadenoma, one gastric cancer and one thyroid cancer. In the endometriosis studies, the frequency of treatment emergent SAEs in the six month treatment period was similar for DMPA-SC and leuprolide: 3.9% (6/152) versus 2.1% (3/143) in Study 270 and 2.3% (3/130) versus 3.0% (4/135) in Study 268.

[18] The Kupperman Index is a global weighted score that evaluates the incidence and severity of 11 hypoestrogenic symptoms, with those related to hot flushes (vasomotor instability) being the most heavily weighted. The hot flush score had a weight of 4; insomnia, abnormal sensations, and nervousness/irritability had a weight of 2; and depression, vertigo, fatigue, pain in the joints/muscles, headache, palpitations, and formication scores had a weight of 1. (Kupperman 1953.)

Table 17. Treatment emergent serious adverse events (ITT population)

System/Organ Class* Preferred Term	All DMPA-SC N = 2053	267BMD	
		DMPA-SC N = 266†	DMPA-IM N = 268
	n	n	n
Subjects with at least 1 serious adverse event	36	10	4
Congenital, familial and genetic disorders			
Dermoid cyst of ovary	0	0	1
Eye disorders			
Retinal edema	1	0	0
Gastrointestinal disorders			
Abdominal mass	1	0	0
Abdominal pain	3	2	0
Gastric ulcer	1	0	0
Hepato-biliary disorders			
Cholelithiasis	0	0	1
Infections and infestations			
Appendicitis	1	1	1
Diverticulitis	1	1	0
Gastroenteritis bacillus	1	0	0
Hepatitis A	1	0	0
Peritonsillar abscess	1	0	0
Pyelonephritis	1	0	0
Pyelonephritis chronic	1	0	0
Staphylococcal infection	1	1	0
Urinary tract infection	1	0	0
Injury, poisoning and procedural compilations			
Drug exposure during pregnancy	1	0	0
Injury	1	0	0
Patella fracture	1	0	0
Road traffic accident	1	1	1
Investigations			
Weight increased	1	0	0

Laboratory findings, vital signs, weight

Laboratory findings

Clinical laboratory assessments (haematology, chemistry and urinalysis) were conducted at baseline and at Months 6 and 12 in the three trials and at Months 24 and 36 in Study 267BMD. Non-fasting lipid profiles were collected in Studies 267 and 267BMD.

There were ten haematology AEs including two cases each of neutropenia and anaemia. There were two cases of "prolonged bleeding time" which are believed to be miscodings for metrorrhagia. There were five AE reports of abnormal liver function tests (LFTs), three of increased blood glucose, three of increased GGT, two of increased bilirubin and one each of increased creatinine, increased AST and increased ALT. There were no relevant urinalysis findings. There were three AEs of increased cholesterol, two each of increased low density lipoprotein (LDL) and increased triglycerides and one of decreased high density lipoprotein (HDL). In Study 268, a full lipid profile under fasting conditions was conducted in two countries in 41 DMPA-SC and 43 leuprolide subjects with sampling undertaken at baseline and at Months 3 and 6. There were some statistically significant changes from baseline in median total cholesterol, HDL and LDL, however the changes were clinically small and levels remained within normal limits.

There were no relevant changes in platelet counts in Studies 267 and 267BMD. In Study 270, a full coagulation profile was undertaken at baseline and at Months 3 and 6 in 36 DMPA-SC and 40 leuprolide subjects. For DMPA-SC subjects, there was a statistically significant reduction in median platelet count (-13.0x10^9) and an increase in median Factor VII and Factor X (clotting factors). In leuprolide subjects, there was an increase in Factor VII, Factor X, protein C and protein S. In the DMPA-SC group, the shift from normal values at baseline to high values at Month 6 occurred in 25% of subjects for fibrinogen, 37.5% of subjects for Factor VII, 59.4% of subjects for Factor X and 9.4% of subjects for antithrombin III (Table 18).

Table 18. Study 270. Coagulation profile shift from normal to high values (ITT population, substudy patients)

Assay	DMPA-SC n/N (%)		Leuprolide n/N (%)	
	Month 3	Month 6	Month 3	Month 6
Platelet count	0/24 (0.0)	0/27 (0.0)	0/31 (0.0)	1/26 (3.8)
PT	025 (0.0)	0/24 (0.0)	2/30 (6.7)	0/24 (0.0)
APTT	0/25 (0.0)	1/24 (4.2)	4/30 (13.3)	2/24 (8.3)
Fibrinogen	2/25 (8.0)	6/24 (25.0)	6/30 (20.0%)	5/24 (20.8)
Factor VII	6/30 (20.0)	12/32 (37.5)	17/38 (44.7)	21/36 (58.3)
Factor X	10/30 (33.3)	19/32 (59.4)	13/38 (34.2)	21/36 (58.3)
Antithrombin III	4/30 (13.3)	3/32 (9.4)	5/38 (13.2)	5/36 (13.9)
Protein C	2/30 (6.7)	1/32 (3.1)	2/38 (5.3)	4/36 (11.1)
Free protein S	2/30 (6.7)	5/32 (15.6)	3/38 (7.9)	3/36 (8.3)

Abbreviations: ITT = intent-to-treat, PT = prothrombin time, APTT = activated partial thromboplastin time

Vital signs

There were no important changes in blood pressure (BP) noted over the 12 months of treatment. The mean change in SBP in DMPA-SC subjects (n=1516) was 1.1 mmHg and for DBP was 0.8 mmHg.

Weight

After 12 months of treatment there was an increase in mean body weight of 1.6 kg in DMPA-SC subjects compared to 2.1 kg for DMPA-IM. After 3 years in Study BMD267, the mean increase was 4.5 kg and 5.8 kg in the DMPA-SC and DMPA-IM groups, respectively. There were 6.9% (140/2043) of women with weight increase reported as an AE and for these women the mean gain was 6.6 kg at Month 12.

Safety in special populations

The incidence of AEs was 59.7% (1004/1683) in White subjects, 54.8% (114/208) in subjects of mixed/multiracial background, 61.0% (61/100) in Black subjects and 71.2% (37/52) in Asian/Pacific Island subjects. The proportion of non-White subjects was too small to enable any definitive conclusions on the effect of race on DMPA-SC safety. There were no data provided on DMPA-SC in adolescents. There were no pregnancies in the contraceptive efficacy trials so there is no information on the effects of DMPA-SC in pregnancy or lactation.

Safety related to drug-drug interactions and other interactions

There were no specific drug-drug interaction studies included with the current Australian submission. The bleeding patterns of subjects who took a CYP3A4 inhibitor or inducer at any time during the course of the study were examined and the overall bleeding pattern was similar in this group to that described for all subjects: a decrease in the number of days and episodes of bleeding and/or spotting and an increase in amenorrhoea over time.

Data on AE rates showed an increase in those taking inhibitors and inducers which may only imply the use was associated with an AE. As the studies were not designed to assess the effect of drug-drug interactions, these results cannot be viewed as conclusive.

Discontinuation due to Adverse Events

Overall 9.9% (203/2053) of the women treated with DMPA-SC withdrew from the studies due to an AE, with the most frequent AEs leading to discontinuation being increased weight (2.0%), intermenstrual bleeding (1.2%), decreased libido (1.1%) and acne (1.0%). The discontinuation rate due to AEs was slighter lower with DMPA-SC than DMPA-IM (17.9% versus 22.2%; Study 267BMD). Discontinuation rates due to an AE were similar for DMPA-SC and leuprolide: 5.4% versus 6.7%, respectively, in Study 268 and 2.0% versus 1.4%, respectively, in Study 270.

Post marketing experience

The current Australian submission refers to two Periodic Safety Update Reports (PSUR) (1 January 2001 to 31 December 2005 and 1 January 2006 to 31 May 2006) that were not provided for evaluation. Two more recent PSURs, dated I January 2006 to 31 December 2008 and I January 2009 to 31 July 2009, were provided for evaluation.

There were 17,400 units of DMPA-SC sold between 2001 and third quarter 2005 and 40 AE cases reported. In the three year report (2006-2008) there were 514,200 units of DMPA-SC sold in the USA (and 33 million units of Depot Provera sold worldwide) with 328 AE cases (15.8% of all MPA cases). In this period there was an increased reporting rate of "incorrect dose" and "underdose" associated with a syringe malfunction with Depo-SubQ Provera marketed in the USA. This was reported as a problem with the needle guard assembly. There was one case of erythema multiforme in a woman who had previously used DMPA-IM without problems. In the six months from 1 January to 31 July 2009, there were 50,500 units of DMPA-SC sold and 65 AE cases reported (15.7% of all MPA cases), 12 of these were serious, and the majority (n=47) were medication errors. The medication errors were mainly incorrect dose and incorrect route or site of administration. There were two cases of unintended pregnancy with DMPA-SC.

A retrospective cohort study assessing the association between DMPA use and bone fractures using the General Practice Research Database (GPRD) in the UK was summarised but was not fully evaluated as the clinical evaluator assumed this would already have been undertaken in relation to DMPA-IM. The study covered 312,395 women using contraceptives in the UK who reported 11,822 factures during the observation period. Fracture incidence was also calculated for a pretreatment baseline period of six months in a sub cohort of women for whom data was available. The study found that women who had "any use" of DMPA had a higher incidence of fracture compared to "never users" (relative risk (RR) 1.41 95% CI: 1.35-1.47). After adjustment for potential confounding factors the IRR was 1.21 (95%CI 1.14-1.28). The risk of axial skeleton fractures, which may be more associated with reduced BMD, was not raised (IRR=0.96 95% CI: 0.73,1.25) while the appendicular skeleton fracture risk was increased (IRR=1.38, 95% CI:1.30,1.46). In a sub-cohort of women for whom data was available prior to commencing DMPA, the risk of fracture "before treatment" was higher than in "never users" (IRR 1.28 95% CI: 1.07-1.53) which possibly indicates that some other factors may be involved in an increased risk of fractures and in the choice of DMPA as contraceptive.

Evaluator's overall conclusions on clinical safety

The primary safety data was pooled from the three contraceptive efficacy trials in 2043 healthy women who received at least one dose of DMPA-SC and for whom AE data were available. There were 1546 women who received four or more injections of DMPA-SC (at

least one year of treatment) which satisfies the minimum data requirement for a new steroid contraceptive according to the TGA-adopted EU guideline (CHMP 2005[19]). The mean age of subjects was 30 years, 82% were White with a mean BMI of 24.3 kg/m^2. Supportive data comes from the 289 subjects who received DMPA-SC in two Phase III endometriosis studies comparing DMPA-SC to leuprolide after 6 months of treatment and 12 months of follow up. BMD was assessed in a specific contraceptive efficacy study as well as in the two endometriosis studies and all DXA scans were analysed centrally. The two larger contraceptive trials were open label with no comparator and the other three Phase III trials were randomised, controlled and investigator blinded.

The overall AE rate was 59.5%, with higher reporting in the Americas (70.7%) compared to Europe and Asia (46.5%), with similar reporting rates seen between racial groups. There was only one death in the clinical program which was considered unrelated to treatment. The incidence of SAEs was low at 1.8% and similar across studies. Notable SAEs in subjects treated with DMPA-SC included: three cases of abdominal pain, three of uterine haemorrhage, two cases each of depression and suicide attempt, one breast cancer and one breast fibroadenoma. Study discontinuation due to AEs occurred in 9.9% of subjects, with the most common reasons being increased weight (2.0%), intermenstrual bleeding (1.2%), decreased libido (1.1%) and acne (1.0%).

Overall, the AE profile of DMPA-SC was consistent with that of DMPA-IM. The most frequent AEs were headache (8.5%), increased weight (6.9%), intermenstrual bleeding (7.1%), amenorrhoea (6.4%), nasopharyngitis (3.9%), vaginal haemorrhage (3.6%), acne (3.3%) and libido decreased (3.1%). Depression was reported as an AE in 3.2% and led to study discontinuation in 0.8% of subjects. Mood disorder was reported in 1.5% of subjects with a discontinuation rate of 0.4%. Breast pain or tenderness was reported in 2.3% of women and there was one CIN Grade III and one invasive ductal carcinoma diagnosed during the study. Injection site reactions (such as lump, dimpling, atrophy, pain) were reported in 6.1% of women with 0.5% withdrawing due to this AE. By contrast, no injection site reactions were reported with DMPA-IM (Study 267BMD)

Weight gain was notable and increased with increasing treatment duration with a mean increase of 1.6 kg at 12 months and 4.5 kg at three years and was the most common AE leading to study discontinuation. There was no notable change in BP over 12 months of treatment.

Bleeding irregularities occurred with DMPA-SC as with DMPA-IM and with longer treatment duration there was an increase in amenorrhoea (56.5% at 12 months) and a reduction in the days of bleeding/spotting. The incidence of amenorrhoea was not affected by BMI. As expected, DMPA-SC resulted in a reduction in endometrial thickness and most women were found to have an atrophic endometrium or have insufficient tissue for diagnosis (78.2%) at 12 months.

There were small number of cases of raised liver enzymes and some significant changes in lipid levels although the levels remained within normal limits. There was no relevant change in platelet count in the contraception studies, while in a subset of women in Study 270 there was a small reduction (-13.0x10^9). There were some alterations in coagulation profiles for which the significance is uncertain. There were no reported thromboembolic events with DMPA-SC (there was one cerebrovascular accident and one deep vein thrombosis (DVT) with DMPA-IM).

The loss in BMD is a known and concerning effect of DMPA-IM and was also seen at similar levels with DMPA-SC in the current evaluation. After 24 months, the median percentage

[19] CHMP. Committee for Medicinal Products for Human Use. Guideline on clinical investigation of steroid contraceptives in women. 2005. EWP/519/98 Rev 1/EMEA/CPMP.

change in the BMD of spine was -4.3% and -5.0% for the DMPA-SC and DMPA-IM groups, respectively. Similarly, in the hip the median percentage change in the BMD was -3.3% and -3.6% for the two groups, respectively. The loss increases with treatment duration and a loss from the spine BMD of ≥ 5% was found in 20.5% and 24.7% after one year and 37.7% and 51.0% after two years in the DMPA-SC and DMPA-IM groups, respectively. At 24 months there were 12.3% of DMPA-SC and 11.8% of DMPA-IM subjects who met the definition of osteopenia with a spine T-score of < -1.0. There were no cases of T-score <-2.5 and no reported osteoporotic fractures. DMPA-SC resulted in a significantly lower reduction in BMD of the spine and femur compared to leuprolide after six months of treatment in both endometriosis trials and there was some reversal of the BMD loss over the 12 months of follow up.

While the AE rate was similar between DMPA-SC and leuprolide, the profile of AEs was different; a significantly higher incidence of intermenstrual bleeding, injection site reactions, pelvic pain, uterine and vaginal haemorrhage was noted with DMPA-SC treatment and a significantly higher incidence of hot flushes, myalgia, toothache and vaginal discharge was noted with leuprolide treatment. Hypoestrogenic symptoms, as measured by the Kupperman Index, showed little change with DMPA-SC but a significant increase with leuprolide. Severe hot flushes (as recorded by the subjects) were reduced or were stable with DMPA-SC treatment but increased notably with leuprolide treatment.

As there were no pregnancies in the contraceptive studies there are no data on the safety during pregnancy or lactation. Studies have not been conducted in teenagers less than 18 year of age so safety in this group is uncertain but expected to be similar to DMPA-IM. Drug-drug interactions were not specifically studied and while there was some reported use of a CYP3A4 inhibitor or inducer at some stage during the trial with no evident effect on bleeding patterns, these results are not conclusive.

Post marketing data on DMPA-SC did not note any additional safety issues. A single case of erythema multiforme was reported. There were syringe malfunction issues in the USA and it is unclear if this will be relevant for Australia. A 2008 retrospective cohort study in the United Kingdom assessing the fracture incidence in women who had reported use of DMPA-IM was included. This study was not evaluated here.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. The following two questions regarding Safety were generated:

1. Are there any data on the use of DMPA-SC in adolescents? If so please provide this information for review.
2. Is the issue with the needle guard noted in the PSURs with the US marketed product relevant to Australia? Please provide comments.

Clinical Summary and Conclusions

The clinical program with DMPA-SC consisted of three Phase I/II pharmacology studies, three Phase III contraceptive efficacy studies and two Phase III endometriosis pain efficacy studies. In all studies, except the dose finding pharmacology study which used the IM formulation, the subcutaneous formulation was used and given at a dose of 104 mg/0.65 mL to the abdomen or anterior thigh. The dosing interval in the multidose studies was 13 weeks ± 1 week. For demonstrating contraceptive efficacy there were two open label, non-comparator, one year studies and one randomised, investigator blinded two year (+ third year extension) study with DMPA-IM as the comparator. These studies included healthy

women aged 18 to 45 years and exclusion criteria were standard for hormonal contraceptives.

The data from one Indonesian site had to be discarded for quality issues and due to the breaking of the evaluator blind. The clinical evaluator also noted a lack of medical review in some places, for example "prolonged bleeding" had not been questioned and so was coded to coagulation issues rather than to menstrual bleeding patterns. Overall, the current Australian submission contained studies that are large, thorough and met the requirements for assessment of new steroid contraceptives.

Pharmacokinetics

Following subcutaneous administration of DMPA, there was a prompt increase in serum concentrations with levels above the therapeutic threshold of 0.2 ng/mL reached within 24 hours. While the single dose PK was characterised by high inter-subject variability, there was prolonged absorption and the MPA trough concentrations on Day 91 (when the next dose would be due), were above the therapeutic threshold.

Subcutaneous injection of DMPA-SC in the anterior thigh resulted in a significantly higher peak MPA concentration than in the abdomen, however there was little difference in MPA trough concentrations (0.41 ng/mL versus 0.47 ng/mL p=0.44) which supports administration at either site.

Race did not appear to have any significant effect on the PK of MPA although the small numbers in each of the five Asian ethnic subgroups did not allow conclusions to be made at this level of specificity. BMI did not have a major effect on the PK of MPA but a trend towards longer T_{max} with increasing BMI was noted and the trough concentration was lower in obese women with BMI >38 kg/m^2 although it remained above contraceptive effect level at 0.26 ng/mL . Given this, dose adjustments based on BMI would not be necessary.

Pharmacodynamics

A serum progesterone level less than 4.7 ng/mL was the main criterion used to assess suppression of ovulation. The dose finding study found that both the 150 mg and 100 mg doses of MPA were effective in suppressing ovulation (if one outlier was removed). The 104 mg DMPA-SC dose suppressed ovulation over the 3 month dosing interval in 62 of 63 women in the two pharmacology studies [one Asian women with increased progesterone did not have evidence of ovulation on other markers tested; E2, LH, FSH, MPA concentration].

Compared to IM DMPA, the SC injection resulted in a longer time to return to ovulation (median 212 days versus 183 days based on serum progesterone). This may be explained by the slower absorption from the SC site and the apparent longer half life following this route of administration (35-47 days SC compared to 13-26 days IM). The earliest ovulation after a single dose was 15 weeks and at 12 months 97% of women (38/39) had returned to ovulation. Data after multiple doses from a small cohort in one of the Phase III trials found the median time to ovulation was 10 months after the last injection with 12/15 (80%) women ovulating within one year.

Although there was no statistical difference between BMI groups, women with a higher BMI tended to have a shorter time to return to ovulation and this correlates with PK finding of lower AUC and C_{min} in this group. Despite this, the 104 mg SC dose was effective at suppressing ovulation over the 3 month dosing interval across all BMI groups.

DMPA-SC inhibited ovulation in Black and Asian women. Black women did show a quicker return to ovulation than White women (190 days compared to 218 days, respectively) but

none did so under 91 days and the sponsor stated the result may have been confounded by BMI. While this is a plausible explanation, this could not be verified.

Clinical Efficacy

For contraceptive efficacy there were 2045 women who received DMPA-SC with a total of 23,025 women cycles of exposure and 19,588 women cycles excluding months where barrier contraception was used or no intercourse occurred. The mean age of subjects was 30.0 years, most were White (82.4%) and the mean BMI was 24.3 kg/m^2.

DMPA-SC was an effective contraceptive with no pregnancies reported in the three trials giving the treatment failure cumulative pregnancy rate was 0% and a Pearl Index of 0.0 pregnancies per 100 woman years (with a reported upper limit of the 95% CI at 0.25 although calculations were not provided). There were however three pregnancies reported: one at 190 days after a single injection; one not detected at enrolment that aborted spontaneously three weeks after the first injection; and one with conception at 72 days post injection in an endometriosis trial. This last case appears to be a treatment failure. There was one pregnancy in a women treated with DMPA-IM with a resultant Pearl Index of 0.28 (95% CI: 0.0, 0.83) pregnancies per 100 women years.

While PK/PD studies indicated no concerning differences in Black or Asian women, the small numbers of these racial groups in the Phase III program limit the ability to make definitive conclusions in these populations. In addition, postpartum women and adolescents were not specifically studied.

Efficacy in endometriosis pain was assessed in two Phase III randomised, investigator blinded trials with the GnRH agonist leuprolide as the active comparator. Women were treated for 6 months and followed for a further 12 months. Daily calcium supplements (500 mg) were provided to all subjects. The studies included otherwise healthy women aged 18 to 49 years with persistent symptoms of endometriosis diagnosed by laparoscopy. Women needed to have a total pelvic score of at least 6 from the 5 categories of endometriosis pain with at least two on dysmenorrhoea, dyspareunia and pelvic pain. There were 573 women included with a mean age of 26 to 31 years and mean baseline total endometriosis pain score of approximately 10 points.

The main analysis assessed non-inferiority to leuprolide based on positive response rates to 4 of the 5 pain categories. The non-inferiority limit was a difference in proportion of subjects improving on 4 items of -20%. This criterion was met in both studies for dysmenorrhoea, dyspareunia, pelvic pain and pelvic tenderness while non-inferiority on pelvic induration was not reached in one study. A reduction of 4 points on the composite score was classed as clinically meaningful and this was found in both studies at Month 6 with a reduction in DMPA-SC treated women of -6.2 and -6.3. The impact on symptom/signs was not as great as seen with leuprolide where reductions of -7.7 (95% CI difference: 0.5, 2.6) and -7.3 (95% CI for the difference: 0.2, 1.9) were found. Treatment with DMPA-SC continued to have an impact on symptoms and signs 12 months after cessation of treatment with mean changes of -5.3 (Study 268) and -6.6 (Study 270). Significant improvement in QoL was also seen using two assessment tools (EPH-30 and SF-36) at Month 6 through to Month 18 in both studies.

It is noted that the drop out rate was higher and the Evaluable population smaller in Study 268. However, the clinical evaluator believed the results were still robust due to the strength of the findings, the consistency across the two studies and the consistency within the population groups analysed.

Clinical Safety

The primary safety data was pooled from the three contraceptive efficacy trials in 2043 healthy women who received at least one dose of DMPA-SC. This included 1546 women who received four or more injections and so had exposure for at least one year of treatment. This adequately meets the TGA-adopted EU guidelines for the minimum amount of safety information for new steroid contraceptives.[19] Supportive data comes for the 289 women who received DMPA-SC in the endometriosis studies. A loss in BMD is a major concern with DMPA-IM and this issue was specifically addressed in one contraceptive study and the two endometriosis studies.

The overall rate of AEs in the contraception studies was 59.5% (1216/2043) and the most frequent were headache (8.5%), increased weight (6.9%), intermenstrual bleeding (7.1%) and amenorrhoea (6.4%), nasopharyngitis (3.9%), vaginal haemorrhage (3.6%), acne (3.3%), libido decreased (3.1%), depression (3.2%) and breast pain/tenderness (2.3%). Study discontinuation due to AEs occurred in 9.9% of subjects with the most common reasons being increased weight (2.0%), intermenstrual bleeding (1.2%), decreased libido (1.1%) and acne (1.0%). These AEs were consistent with the product labelling for DMPA-IM. However, unlike DMPA-IM where no injection site reactions (such as lump, dimpling, atrophy, pain) were reported, these occurred in 6.1% of women receiving DMPA-SC. Weight gain was notable and increased with treatment duration with a mean increase of 1.6 kg at 12 months and 4.5 kg at 3 years. Amenorrhoea was frequent and by 12 months was reported in 56.5% of women.

The incidence of SAEs was low at 1.8% and in particular included three cases of abdominal pain, three of uterine haemorrhage, two cases each of depression and suicide attempt, one breast cancer and one breast fibroadenoma. There was only one death. There were no thromboembolic events with DMPA-SC although women with such a history were excluded from the trials.

Loss of BMD was seen at similar levels with DMPA-SC and DMPA-IM and the loss increased with treatment duration. There were 12.3% of DMPA-SC and 11.8% of DMPA-IM subjects who met the definition of osteopenia with a spine T-score of < -1.0 at 24 months. There were no cases of T-score <-2.5 and no reported osteoporotic fractures. Compared to leuprolide, DMPA-SC resulted in a significantly lower reduction in BMD of the spine and femur after 6 months of treatment in both endometriosis trials and there was some reversal in this BMD loss over the 12 months of follow up.

DMPA-SC and leuprolide has similar rates but differing profiles of AEs: a higher incidence of intermenstrual bleeding, injection site reactions, pelvic pain, uterine and vaginal haemorrhage were noted with DMPA-SC and a higher incidence of hot flushes, myalgia, toothache and vaginal discharge occurred with leuprolide. DMPA-SC did not result in the hypoestrogenic symptoms that were seen with leuprolide.

Benefit risk assessment

Benefits

DMPA-SC was shown to be a very effective contraceptive and this efficacy has been achieved with a lower dose than the IM formulation. This efficacy was maintained across women with differing BMI. The three monthly dosing is convenient and useful for increasing compliance and the SC route of administration also offers the possibility for women to self-administer the injection although self-administration is not being sought in this application.

DMPA-SC did not affect blood pressure and progestin only contraceptives may have a lower risk of adverse cardiovascular outcomes than oestrogen-progestin combinations

(WHO 1998[20]) and so could be considered a benefit for women with a history of thromboembolic disorders (ACOG 2006[21]). There is, however, no data in this group as they were excluded from the efficacy trials.

Amenorrhoea may be viewed as a benefit by some women and would be useful in women with menorrhagia or dysmenorrhoea or those needing menstrual suppression. Protection against endometrial hyperplasia and reduced risk of endometrial cancer has been noted with DMPA-IM (WHO 1991[22]) and it is assumed this could also occur with DMPA-SC.

For endometriosis associated pain, DMPA-SC was an effective treatment with response rates in line with the GnRH agonist leuprolide and clinically meaningful reductions in signs and symptoms and improvement in quality of life. The relative reduction in pain was however less than that seen with leuprolide. It was also encouraging to see the treatment effect continue after cessation for as long as the next 12 months. Both endometriosis treatments resulted in BMD loss and an important benefit of DMPA-SC was that the bone loss was significantly less after 6 months of treatment compared with leuprolide. In addition, DMPA-SC treatment resulted in less hypoestrogenic symptoms and hot flushes.

Risks

The major risk with DMPA-SC use is BMD loss, as has been noted with DMPA-IM. There was some evidence from the endometriosis trials that on cessation of DMPA-SC bone loss was largely regained after 12 months. Epidemiological studies of DMPA-IM support a significant reversal after ceasing treatment (Kaunitz 2006[23], Scholes 2002[24], Scholes 2005[25]). Nevertheless, BMD loss is a particular concern in adolescents as they would not yet have attained their peak bone mass and in peri menopausal women who may not have the opportunity to regain lost bone mass prior to menopause. From the data provided, it is not possible to say whether this reduction in BMD translated to an increased risk of fractures. The epidemiological study in the UK using the General Practice Research Database (GPRD) found women reporting "any use" of DMPA-IM did have an increased fracture risk compared to "never users", though the risk was present prior to DMPA use and in the non-axial skeleton, rather than the axial skeleton, indicating some other factors apart from DMPA may be involved in increasing the fracture risk.

Despite the lower dose of MPA in the SC formulation, the adverse event rate was similar to the IM formulation and so there appears little safety advantage of the new formulation. The main adverse effects were similar to DMPA-IM and included menstrual irregularities, weight gain and headaches. Increased weight, intermenstrual bleeding, decreased libido

---

[20] WHO. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Contraception* 1998 May; 57(5):315-24.

[21] ACOG (American College of Obstetricians and Gynaecologists) practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions*. Obstet Gynecol* 2006; 107:1453.

[22] World Health Organization. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer.* 1991 Sep 9;49(2):186-90

[23] Kaunitz AM; Miller PD; Rice VM; Ross D; McClung MR. Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. *Contraception*. 2006 Aug; 74(2):90-9.

[24] Scholes D; LaCroix AZ; Ichikawa LE; Barlow WE; Ott SM. Injectable hormone contraception and bone density: results from a prospective study. *Epidemiology.* 2002 Sep; 13(5):581-7.

[25] Scholes D; LaCroix AZ; Ichikawa LE; Barlow WE; Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. *Arch Pediatr Adolesc Med* 2005 Feb; 159(2):139-44.

and acne were the most common adverse effects resulting in treatment discontinuation. The main difference between formulations was that the SC formulation resulted in more injection site reactions (6% versus 0%) and, while none were considered serious, 0.5% of women withdrew because of them. There was one breast cancer reported in the program so this potential risk cannot be ruled out.

There is a risk that contraceptive efficacy may fail if women do not return for the next injection at the scheduled time. Typical user failure rates were not provided but it would be anticipated they would be similar to DMPA-IM where user failure is not high and approaches method failure (US product information). It is known that DMPA-IM results in a slow return to ovulation and fertility and, whilst data on this was limited in the current Australian submission, the same appears to apply to DMPA-SC.

There were no specific studies on drug-drug interactions so the effect can only be extrapolated from data with DMPA-IM. There were low numbers of non-white women in the clinical program, no adolescents or no post-partum women so definitive conclusions in these populations cannot be drawn.

Balance

Contraception

DMPA-SC has been shown to be a very effective, convenient contraceptive, which is reversible, albeit slowly. The subcutaneous administration allows relative ease of administration. However, in spite of the lower dose of the DMPA-SC than the DMPA-IM, DMPA-SC does not result in a lower adverse event rate and produces more injection site reactions. DMPA-IM is a well accepted contraceptive with a long and established risk profile. Given the same active ingredient and systemic administration, there is no reason to believe this information would not be directly applicable to DMPA-SC.

There is a significant risk of BMD loss with DMPA-SC and women need to be advised to ensure adequate intake of calcium and vitamin D together with regular exercise. Other contraceptive alternatives should definitely be considered if there are risk factors for osteoporosis present. To limit potential BMD loss, it is recommended that treatment be limited to two years duration unless there are no alternatives. DMPA-SC was not studied in adolescents so use in this group of women should be avoided unless no other methods are felt appropriate.

The clinical evaluator noted and agreed with the “Black Box” warning on the US PI in relation to bone loss. On balance, DMPA-SC does have contraceptive advantages that outweigh the skeletal risk as long as this is backed by detailed and appropriate labelling and ongoing monitoring of fracture risk.

Endometriosis

Endometriosis is a chronic disease which can have a significant impact on a woman’s quality of life. The main aim of treatment is to address the associated pain and subfertility. Treatment may be surgical and or pharmacological (such as combined oestrogen-progestin pills, progestins, danazol, gestrinone and GnRH agonists) and is aimed at reducing the levels of ectopic endometrial tissue activity. As there is limited evidence of treatment superiority, cost, side effects and personal preference often dictate which of the pharmacological treatments is chosen.

DMPA-SC was found to be an effective treatment for endometriosis associated pain with response rates in line with leuprolide, although the level of effect was less. In addition, the efficacy and improved quality of life continued after treatment cessation for the next 12 months. While DMPA-SC does produce significant side effects (such as weight gain and

irregular bleeding) it produced less hypoestrogenic symptoms, less hot flushes and, in particular, less associated bone mineral density loss than leuprolide. DMPA-SC therefore offers an effective treatment alternative in endometriosis with a lower risk of bone loss than the GnRH agonist leuprolide.

Conclusions

It was concluded that the overall benefit risk balance of Sayana is positive for the proposed indication of:

> ***Endometriosis****: For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy or for the control of symptoms when surgery is contra-indicated or has been unsuccessful.*
>
> ***Contraception (ovulation-suppression):*** *For the long-term prevention of pregnancy in women when administered at 3-month intervals.*
>
> *Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use SAYANA long term (greater than two years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density.*

Conditions for registration

It was recommended that approval of Sayana be subject to incorporation of the suggested changes to the proposed product information and satisfactory answers to the questions listed above (under *List of Questions*).

V. Pharmacovigilance Findings

The active ingredient for Sayana (medroxyprogesterone acetate) is the same active ingredient used for Depot Provera injection 50 mg/1mL. Depot Provera is given as 150 mg/mL dose intramuscular every three months. The proposed indications for Sayana are the prevention of pregnancy and for treatment of endometriosis, which are the same indications for Depot Provera. The proposed dosage is 104 mg to be given every three months via subcutaneous injection, which is applicable to both indications.
In terms of formulation, the Sayana formulation is almost identical to the formulation for Depot Provera, with the two exceptions:

- There is a lower dose of medroxyprogesterone acetate in Sayana compared with Depot Provera
- Sayana contains the excipients sodium phosphate, methionine, povidone and sodium hydroxide

The main changes to the registration of MPA are reduced dose and change in the route of administration from IM to SC injection. It is noted that the formulation Sayana contains additional excipients, which by definition are inactive and should not confer any biological activity. These changes are minor and should not modify the benefit/risk ratio of the product. Therefore no evaluation of the Risk Management Plan (RMP) was required by the TGA.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator noted that the preservatives are here characterised as "suspending agents" and that their selection was empirically based. Methionine is a new excipient. The proposed limits of degradation products were accepted on toxicological grounds.

A shelf life of three years below 25°C, not frozen, has been supported.

The formulation that was used in the Phase III efficacy studies is the same as the one proposed for marketing.

Bioavailability

As noted by the quality evaluator, "The proposed Sayana product is to be indicated for the same endometriosis and contraception (ovulation suppression) indications (only). Thus, unless there [are] clinical data to independently support these indications, bioequivalence of the two formulations and routes of administration will be important."

One study, Study 839-FEH-0012-271, was evaluated. It only compared Sayana given at two sites and it suggested more extensive absorption from the leg than from the abdomen, particularly in the first 30 days. These differences are obvious but were not extensively explored (see Figure 2 above).

The clinical evaluator also reviewed this study (see below).

The data package did not include a direct bioequivalence study between the registered formulation, given intramuscularly, and the new formulation, given subcutaneously at each of the two proposed sites.

Recommendation

The application has not been considered by the Pharmaceutical Subcommittee.

The quality evaluator recommended registration on quality grounds but has left the bioavailability issues as clinical ones:

"In relation to bioavailability:

- The PI states that the product can be administered into the anterior thigh or the abdomen. The responses from these two sites have not been shown to be bioequivalent, but the sponsor argued that this is a not an issue as the Day 91 C_{min} results are similar.
- No data have been provided which compare SC administration to IM administration, but the sponsor argued that this was not intended, anticipated or necessary for this submission."

The Delegate noted that the application has a number of bioavailability issues associated with it.

Nonclinical

The nonclinical evaluator noted that the data package is GLP-compliant as far as one local tolerance (subcutaneous route) study in rabbits is concerned but not in regard to the bulk of nonclinical studies because these nonclinical studies predated GLP requirements.

The nonclinical evaluator noted that human exposure is proportionately less with Sayana than with Depo-Provera, "the maximum recommended dose of Sayana (104 mg SC) is less than that for Depo-Provera, the existing product for IM injection (150 mg). $AUC_{0-\infty}$ is ~12–30% lower and C_{max} is ~60% lower." [That is, the exposure is not necessarily proportionately lower by extent of absorption.]

The application's salient points were summarised in these terms:

- the dose of medroxyprogesterone acetate is lower for Sayana versus Depo-Provera (106 mg SC versus 150 mg IM, administered once every 3 months) so resultant exposure is also less;

- the strength of the active ingredient is proportionately higher with the new product (160 mg/mL compared to ≤150 mg/mL); and,

-the excipient profile is altered.

No specific or new toxicological findings were noted. Local tolerance in rabbits was acceptable (slight signs of inflammation) after subcutaneous dosing at the full human dose (0.65 mL). Inadvertent intradermal administration was less well tolerated, producing minimal to slight injection site reactions (erythema/oedema), slight degeneration of adjacent connective tissue and slight focal myositis in the cutaneous muscle.

There were no nonclinical objections to the registration of Sayana for the proposed indications.

The Delegate noted that no new toxicological data of significance have emerged in respect to MPA as a single agent. Local inflammatory effects of Sayana seem to be minor.

Clinical

The clinical evaluator noted that the proposed formulation is intended among other things for self-administration.

Three Phase I/II clinical pharmacology studies were submitted. All studies were single dose studies.

Pharmacokinetic/bioavailability Data

In Study **265**, the pharmacokinetics of four doses of MPA were examined after a single subcutaneous dose in 46 healthy women aged 18 to 45 years. The study was of parallel group design, that is, no woman received more than a single dose. There were also pharmacodynamic endpoints (ovulation). The mean (standard deviation (SD)) serum MPA concentrations at Day 91 (proposed as the dosing interval) were 0.174 (0.082), 0.253 (0.111), 0.332 (0.137) and 0.495 (0.215) ng/mL in the 50 mg, 75 mg, 100 mg, and 150 mg dose groups, respectively. At Day 91, MPA levels were above the 0.20 ng/mL threshold for ovulation suppression in the 100 mg and 150 mg dose groups.

The Delegate noted that dose proportionality was relevant to the application. Unfortunately, this study used a slightly different formulation which is not intended for marketing (100 mg/0.5 mL IM formulation).

Study 271 was an endometriosis study that also assessed the pharmacokinetics of a single dose of 104 mg/0.65 mL in 24 healthy "Asian" women aged 18 to 40 years. Asian here means: four Chinese, two Filipino, ten Indian, six Malayan and two Thai women with a mean age of 33.8 years and a mean BMI of 22.4 kg/m^2.

Consistent with the quality evaluator, the clinical evaluator concluded that SC injection of Sayana in the anterior thigh resulted in a higher C_{max} than in the abdomen (1.65 versus 0.94 ng/mL, p=0.002) however there were no differences in MPA trough concentrations (C_{91}) (0.41 ng/mL versus 0.47 ng/mL respectively, p=0.44). A similar trend was also noted in Study 265.

In Study 271, progesterone concentrations were suppressed in 23 of 24 women for at least 112 days. One Filipino woman had a serum progesterone of 16 ng/mL on Day 57. Levels of E2, LH, and FSH in this woman did not support ovulation and her MPA level on Day 91 was also above the threshold at 0.438 ng/mL.

In Study **272**, there were 42 healthy women aged 18 to 40 years (one Asian, fourteen Black and 27 Caucasian) who received a single dose of Sayana or Depo-Provera and contributed pharmacokinetic data (but only for Sayana) although the primary purpose of this study was to assess time to return to ovulation. The treatment groups received Sayana 104 mg/0.65 mL or Depo-Provera 150mg/1 mL (anterior thigh or abdomen) as a single dose only, with a randomisation ratio of 2:1 SC:IM. These women also had vaginal ultrasound examinations to determine ovarian follicle growth and endometrial thickness.

In Study 272, after a single injection of DMPA the first occurrence of ovulation (based on serum progesterone levels) was on Day 106 in the Sayana group and on Day 70 in the Depo-Provera group. Twelve months after a single injection, 38/39 (97.4%) women in the Sayana and 18/19 (94.7%) in the Depo-Provera group had returned to ovulating.

In comparison, in the Phase III Study 267BMD, MPA trough (C_{min}) levels were analysed after 6, 12 and 24 months of treatment in women who had received Sayana (104mg) and Depo-Provera (150mg) (Table 19).

Table 19. Study 267BMD.

MPA C_{min} values, summary statistics by visit (ITT population)

Visit	MPA C_{min} (ng/mL)	DMPA-SC	DMPA-IM
Month 6	Mean (SD)	0.666 (0.363)	0.803 (0.467)
	Median	0.583	0.750
	Range	0.179 - 2.350	0.000 - 2.760
	Total Reported	157	147
Month 12	Mean (SD)	0.794 (0.365)	0.790 (0.367)
	Median	0.728	0.770
	Range	0.201 - 2.810	0.000 - 1.720
	Total Reported	144	140
Month 24	Mean (SD)	0.874 (0.331)	1.028 (0.452)
	Median	0.822	1.060
	Range	0.200 - 1.740	0.000 - 2.210
	Total Reported	106	99

Abbreviations: ITT = Intent-to-treat, SD = standard deviation

Table continued on the next page.

Table 19 continued.

Study 267BMD. MPA C_{min} values, change from Month 6 visit (ITT population)

Visit	MPA C_{min} (ng/mL)	DMPA-SC	DMPA-IM
Month 6	Month 6 Mean (SD)	0.666 (0.363)	0.803 (0.467)
	Month 6 Median	0.583	0.750
	Total Reported	157	147
Month 12	Month 6 Mean (SD)†	0.690 (0.373)	0.818 (0.451)
	Mean (SD)	0.058 (0.415)	-0.071 (0.508)
	Median	0.093	-0.002
	Range	-1.626 - 1.630	-2.354 - 0.846
	Total Reported	106	100
Month 24	Month 6 Mean (SD)†	0.728 (0.443)	0.848 (0.501)
	Mean (SD)	0.153 (0.443)	0.163 (0.554)
	Median	0.156	0.210
	Range	-1.160 - 1.132	-1.816 - 1.531
	Total Reported	81	78

† Summary statistics of the Month 6 visit values for subjects having non-missing values at both the Month 6 visit and the change visit

Cross-study comparisons suggest consistency in results. An analysis of pooled data suggested that severe obesity (BMI >38 kg/m^2) was associated with lower trough levels of MPA although they remained above the contraceptive effect level at 0.26 ng/mL.

Pharmacodynamic Data

The clinical evaluator reported that data on concentration response relationships were not provided in the current Australian submission. However, based on previous studies, serum MPA levels at or above 0.2 ng/mL are needed to suppress ovulation in nearly all women and this informed dose selection. The clinical evaluator concluded that, compared to Depo-Provera, the SC injection resulted in a longer time to return of ovulation (median 212 days versus 183 days based on serum progesterone). This may be explained by the slower absorption from the SC site and the apparent longer half life (35-47 days after SC injection compared to 13-26 days following IM administration).

Ovarian activity was inferred from ovarian hormonal activity as sampling was too infrequent to define FSH and LH peaks.

No specific studies were undertaken to examine pharmacokinetic or pharmacodynamic interactions. The Phase III studies had no reports of pregnancies.

Dose Finding/Efficacy

The clinical evaluator concluded; *the 100 mg dose suppressed ovulation in all women when one outlier was removed and also maintained the MPA concentration above the threshold level of 0.20 ng/mL at Day 91. The sponsor suggested that the subject with the unusual MPA PK profile may have been due to injection close to or into a blood vessel. … This translates to a potential risk of one in 200 (0.5%) of method failure which, while not ideal, is acceptable for such a contraceptive. From this study the clinical evaluator concluded that 100 mg is the most appropriate dose to use in the Phase III program and the pharmacodynamic effect of this dose at suppressing ovulation was further confirmed in Studies 271 and 272…*

Phase III Studies

There were two open, non-comparative Phase III efficacy and safety studies for the contraception indication and two single blinded, randomised, comparative (against leuprorelin) Phase III studies for the endometriosis indication.

Contraception

Study 267 was conducted between 2001 and 2002 in 74 centres in six countries in the Americas. Women received MPA 104 mg/0.65 mL packed in a prefilled syringe and given subcutaneously to the anterior thigh or abdomen every 3 months for one year, beginning in the first 5 days of a normal menstrual cycle.

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at one year was 0% and the Pearl Index was 0 pregnancies per 100 women years. Confidence intervals were not calculated in the current Australian submission. One woman, who was pregnant at entry (with a negative pregnancy test) miscarried.

The above study included a comparative extension substudy (267BMD) that examined the effects on bone mineral density of Sayana versus Depo-Provera.

Study 269 was conducted between 2001 and 2002 at 64 sites in 11 Eurasian countries. The study design was very similar to that of Study 265. Some 61.6% of the women self-injected at least once and 19.5% did so at home. Compliance was high.

Efficacy results were as above, with no confidence intervals reported.

Study 267BMD was a three year substudy of the primary 12 month contraception efficacy trial Study 267. It was a randomised, investigator blinded trial of Sayana and Depo-Provera in women aged 18 to 35 years with the primary objective to evaluate BMD changes at one, two and three years relative to baseline. "Recovery" BMD changes were evaluated one year after ceasing DMPA for those continuing in the study off treatment in Year 3. The primary efficacy endpoint was the treatment failure cumulative pregnancy rate at two years. The primary safety variable was the percentage change from baseline in BMD after two years of treatment. There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the Sayana women became pregnant while one of the Depo-Provera women became pregnant and this subject discontinued the study at 21 months.

Combing the above results, the efficacy of Sayana was greater than for Depo-Provera where there was one pregnancy with a Pearl Index of 0.28 pregnancies per 100 women years (95% CI: 0.0, 0.83).

The applicant was asked to confirm that this "substudy" was in fact separate to Study 267 in the sense that women did not receive a year of Sayana in the main study before enrolment in Study 267D.

Overall, the clinical evaluator found that Sayana was an effective contraceptive.

Endometriosis

There were two single blinded, randomised, comparative (against leuprorelin) studies to support this indication.

Study 268 was conducted at 43 centres in the US and 7 centres in Canada between 2001 and 2003. The primary objective was the assessment of equivalence in the reduction of endometriosis associated pain, using a composite pain score. The primary safety objective was the demonstration of superiority of Sayana over leuprorelin for minimising BMD decline after 6 months of treatment.

The clinical evaluator noted that, "The sample size was smaller than desired (274 instead of 320) with 136 DMPA-SC and 138 leuprorelin subjects in the ITT population and 65 and 77 respectively in the Evaluable population (compared to the desired 105 per group)." As a clinical opinion, the non-inferiority criteria were met for dysmenorrhoea, pelvic pain and pelvic tenderness.

Study 270 was similar to Study 268 above and it was conducted between 2001 and 2003 at 37 centres in 12 countries. Equivalence was reported for the primary endpoint, "In the ITT population at 6 months, all 5 signs and symptoms of endometriosis were statistically non-inferior to leuprolide with the lower limit of the 96% CI of the difference in proportion responding (at least one score level) being above -20% ($p<0.02$)."

Overall, the clinical evaluators found that Sayana showed some efficacy as a treatment for endometriosis but there are some limitations on this, "While DMPA-SC met the non-inferiority criteria on the responder rates and resulted in clinically meaningful reduction in the symptoms and signs of endometriosis, the response to treatment was significantly greater with leuprolide (95% CI for the difference in composite score at Month 6 for Study 268 was 0.5 to 2.6 and for study 270 was 0.2 to 1.9)." "...the evaluator believes the results are robust due to the strength of the findings, the consistency across the two studies and the consistency within the population groups analysed." "The relative reduction in pain was, however, less than that seen with leuprolide."

The Delegate noted that both of these studies were underpowered. Study 268 is so underpowered that it cannot claim non-inferiority. However, it is supportive of some efficacy. Of note, there was one pregnancy reported with Sayana in these two studies with conception at 72 days after injection. This case appears to be a treatment failure.

Safety

In the contraception studies, 2043 women received Sayana and 268 received Depo-Provera whereas in the endometrial efficacy studies it appears that adverse events were reported in 219 women who received Sayana versus 208 who received leuprorelin, both groups corresponding to similar proportions of those randomised. There were 1388 (67.6%) women who received four and a further 158 (7.7%) who received five or more Sayana injections. Overall, 9.8% of enrolled women withdrew due to adverse events. The AE profile of Sayana was consistent with that of Depo-Provera.

The most frequent adverse events (≥5% of subjects) in women receiving Sayana were headache (8.5%), increased weight (6.9%), intermenstrual bleeding (7.1%) and amenorrhoea (6.4%). Serious adverse events included one Cervical Intraepithelial Neoplasia Grade III and one invasive ductal carcinoma diagnosed during the study.

The Delegate noted that the frequent events are reactions, not events.

As noted by the clinical evaluator, depression was reported in 3.2% (65/2043) of women and resulted in discontinuation in 0.8%. Mood disorder was reported as an adverse event in 1.5% and a reason for discontinuation in 0.4% of subjects.

Common adverse reactions leading to withdrawal from the studies included acne, weight increase, libido decreased and intermenstrual bleeding.

In regard to bone mineral density:

- The change in BMD was assessed In Study 267BMD at 12, 24 and 36 months and in the endometriosis Studies 268 and 270 at 6, 12 and 18 months. MPA by both routes was associated with similar BMD losses.
- In the endometriosis studies, the BMD reduction was less with Sayana than with leuprorelin. [The data are reported as ITT, not per protocol, however. This may underestimate the effects of treatment.] Sayana showed, after 6 months of treatment, a median change in hip BMD of -0.4% for the hip and -1.0% for the spine. Sayana resulted in a significantly lower reduction in BMD of the spine and femur compared to leuprorelin after 6 months of treatment in both endometriosis trials and there was some reversal in this BMD loss over the 12 months of follow up.

- At Month 18, 12 months after cessation of study medication, spine BMD had **recovered** close to baseline in the Sayana group and, while improved, was still reduced from baseline in the leuprorelin group (median change 0.2% versus -1.7%, p=0.021).

Recommendations of Clinical Evaluator

Overall, the clinical evaluator concluded that the overall benefit-risk balance was positive for Sayana:

- for contraception provided that the "Black Box" warning in the US PI in relation to bone loss is included in the PI. On balance, Sayana does have contraceptive advantages that outweigh the skeletal risk as long as this is backed by detailed and appropriate labelling and ongoing monitoring of fracture risk.; and
- for endometriosis associated pain with response rates in line with leuprorelin, although the level of effect was less.

The indications proposed by the clinical evaluator match those proposed by the sponsor.

Risk Management Plan

No special risk management was proposed for Australia and none has been requested by the Office of Product Review. The clinical evaluator noted that the EU RMP includes a protocol and results of a comparative study of the effect of Depo-Provera on the incidence of bone fracture in the UK using the General Practice Research Database (GPRD).

Risk-Benefit Analysis

Delegate Considerations

A key issue with this application is the relative bioavailability versus the current dose that is given intramuscularly and the correct dosing interval. Because of the lack of direct comparisons with Depo-Provera, Sayana has been developed as a standalone product. Pharmacodynamic data support the dose chosen for Sayana but the Phase III studies cannot be used to make comparisons with Depo-Provera. However, all safety issues are likely to be common except those specific to the site of administration. On balance, Sayana is a therapeutic alternative to Depo-Provera.

The adopted guideline on steroidal contraceptives does allow for some latitude:

> "**Reduced requirements in special circumstances**
>
> In case of minor modifications of existing products, a lower number of cycles may be required provided that:
>
> • pharmacodynamic studies show at least an equivalent effect on ovarian function compared with the existing product
>
> • the reference method has a well documented efficacy";

and,

> "The duration of efficacy studies should be six months to one year or more. For any new contraceptive, at least 400 women should have completed one year of treatment.
>
> For long-acting products (such as. implants, medicated intra-uterine devices (IUDs)) the study duration should cover the claimed duration of effectiveness. For long-acting products, intended to be used for more than three years, the number of women completing the claimed duration of use should be at least 200."

The indication relating to endometriosis is based on one markedly underpowered study and one slightly underpowered study that at least show consistent trends. The Advisory Committee for Prescription Medicines' (ACPM's) advice was sought on the adequacy of the data to support efficacy. In women with endometriosis who are at risk of osteoporosis, danazol is probably a better choice than depot MPA or a GnRH agonist. Unfortunately, this has not been studied.

There are statistical issues with this application:

1. The use of ITT and not per protocol (PP) analyses in non-inferiority studies;
2. The lack of a 95% upper limit of the CI in the Pearl Index;
3. The extensive analyses of underpowered studies in endometriosis when not even the primary endpoint could be reported.

Self-administration is not proposed and the Delegate endorsed this decision.

The Delegate proposed that the application be approved.

The registered indication should be:

> ***Endometriosis****: For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra- indicated or has been unsuccessful.*
>
> ***Contraception*** *(ovulation suppression): For long-term prevention of pregnancy in women when administered at 3-month intervals.*
>
> *Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use Sayana long-term (greater than two years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (See PRECAUTIONS).*

Response from Sponsor

Issues raised in the Delegate's Overview for consideration by the ACPM are highlighted as text in italics and Pfizer's response appears in normal text.

Issues raised in the Delegate's Overview

1. In relation to bioavailability:

The PI states that the product can be administered into the anterior thigh or the abdomen. The responses from these two sites have not been shown to be bioequivalent, but the company argues that this is not an issue as the C_{min} Day 91 results are similar.

The pivotal clinical studies were conducted using abdomen and anterior thigh as "permitted" injection sites, with the abdomen being the site that was predominantly used in both studies (66.3% of injections In Study 267; 62.5% of injections In Study 269). It is known that the observed efficacy of the product was equal at these two sites, since no contraceptive failures occurred in these two pivotal contraception studies. Therefore, while a formal comparison of the PK profiles between the two injection sites was not conducted, it is reasonable to conclude that both injection sites provided adequate MPA levels during the 90 day treatment period. Since effective PK profiles were produced at both the thigh and the abdomen, it can be concluded that both PK profiles were sufficient for efficacy. Bioequivalence of the two profiles cannot be concluded, but bioequivalence of the two profiles was not an objective of the studies.

The objective of the studies was to demonstrate that the product is safe and effective when these two sites are used for injection and safety and efficacy data were provided based on a study design wherein both sites were utilised. In addition, the pivotal contraception trials for depomedroxyprogesterone acetate – subcutaneous (DMPA-SC) were conducted in a manner that demonstrated the safety and efficacy of the product without any reference to medroxyprogesterone acetate – intramuscular (DMPA-IM).

No data have been provided comparing SC administration to Intramuscular (IM administration, but the sponsor argued this is not intended, anticipated or necessary for this submission.

DMPA-SC was studied independently of DMPA-IM because it was recognised that DMPA-SC 104 mg was not likely to be bioequivalent to DMPA-IM. There is no head to head IM versus SC PK study from which to conclude that the two formulations are not bioequivalent but the data from separate studies suggest that the serum MPA levels after IM injection (150 mg) rise higher, initially, and fall off somewhat faster that serum MPA levels after SC injection (of 104 mg), but with the result that, at the end of the 90 day treatment period, both provide similar serum MPA levels on Day 90 (about 0.4 ng/mL, on average) and show similar, essentially complete, contraceptive efficacy.

That is, the main concern was that the SC formulation would be as effective as the IM formulation; and with zero contraceptive failures in the Phase III program for DMPA-SC 104 mg, it can reasonably be concluded that DMPA-SC is at least as effective as DMPA-IM.

With regard to safety, the main pharmacodynamic safety endpoint is bone mineral density (BMD) change. The two formulations were directly compared In Study 267BMD for BMD changes. At 12 months, there was less BMD loss with the SC product ($p<.05$). This finding does seem congruent with the serum MPA levels being somewhat lower with SC during the early part of the 90-day period. However, over time (that is, out to the second and third year) this difference in BMD decline disappears and the two products show BMD changes that are "not statistically significantly different". To the extent that the serum MPA profiles for SC and IM might be somewhat different, at least early on, it does appear that bone cannot distinguish between the two serum profiles over time.

Thus, the early BMD data are consistent with somewhat lower exposure from the SC formulation and emphasises that the two formulations would likely not be bioequivalent, but that this difference - if it exists - is not sufficient to result in any meaningful difference in BMD effect over time. Thus, the BMD data, along with the pregnancy data, can be interpreted to mean that the two formulations are "similar" or "functionally equivalent" in terms of efficacy and systemic (BMD) safety. This does not mean that they are "bioequivalent" on the basis of serum levels within the 80-125% margins. We have not shown that they are bioequivalent according to these margins but, since the safety and efficacy of each formulation have been demonstrated independently in adequate and well-controlled pivotal trials, Pfizer proposed that there would be no requirement to show bioequivalence according to the 80-125% margin.

2. The applicant is asked to confirm that substudy 267BMD was in fact separate to Study 267 in the sense that women did not receive a year of Sayana in the main study before enrolment in 267D.

Study 267BMD (3-year BMD) is completely independent of Study 267 (1-year contraception) and there is no overlap in the study populations between the two studies.

3. Endometriosis. Both of these studies are underpowered. Study 268 is so underpowered as to be useless for claiming non-inferiority. However, it is supportive of some efficacy. Of note,

there was one pregnancy reported with Sayana in these two studies with conception at 72 days after injection. This case appears to be a treatment failure.

Both of the pivotal efficacy studies for endometriosis (Study 268 and Study 270) followed a similar statistical plan, reproduced here from the protocols:

6.7.2. Determination of Sample Size

The sample size calculations were performed using nQuery version 4.0 software. The sample size was primarily estimated using a test of equivalence for improvement rate after 6 months of therapy in each sign/symptom score (including dysmenorrhoea, dyspareunia, pelvic pain, induration, and pelvic tenderness) as evaluated using the modified Biberoglu and Behrman scale, which had scores from 0 to 3. Using a 2-sided test level of 4% for each symptom and a desired statistical power of 80% (under the assumption that each treatment group would yield at least a 50% response rate), 105 evaluable patients per treatment group who completed 6 months of study treatment were required for a determination of equivalence between the 2 treatment groups to within 20%. An adjustment of Type I error for multiple comparisons was made using the Hailperin-Ruger method of adjustment.

Assuming a dropout rate of 35% after 6 months of treatment, 160 patients must have been enrolled in each treatment group.

Thus, in order to achieve the statistical power called for in the protocol, each study would have needed to achieve 105 completers (per group). In Study 268, there were 88 completers in the DMPA-SC group and 102 completers in the leuprolide group, and this study was under-powered according to the statistical plan – marginally so in the leuprolide group, but more clearly so in the DMPA-SC group. In Study 270, which had an identical statistical plan, there were 138 and 136 completers in the DMPA-SC and leuprolide arms of the study, and this study does not appear to be underpowered according to our interpretation of the statistical plan.

In the contraception studies, where pregnancy was the primary endpoint, there were no contraception failures – and none would be anticipated if efficacy was assumed to be similar to the known efficacy of DMPA-IM. There was, indeed, one contraceptive failure in the endometriosis program. While contraception was not an efficacy endpoint in this endometriosis trial, we would agree that this contraceptive failure would not be anticipated, based on the pharmacology of the drug. This finding is quite unusual and cannot be explained on the basis of the available data; it is possible that the injection was not properly administered but this is speculation and cannot be confirmed. By way of context, in a pivotal contraception trial of an oral contraceptive, approximately 1% contraceptive failures would be expected. Therefore, among the 2500 or so subjects in combined Phase III studies (Studies 267, 268, 269 and 270), approximately 25 contraceptive failures would be anticipated across these four studies if that 1% incidence rate applied, while the actual number of failures was one.

4. Overall, the evaluator concluded that the overall benefit-risk balance is positive for Sayana

For contraception provided that the black box warning in the US PI in relation to bone loss is included in the PI. On balance, Sayana does have contraceptive advantages that outweigh the skeletal risk as long as this is backed by detailed and appropriate labelling and ongoing monitoring of fracture risk; and

For endometriosis associated pain with response rates in line with leuprorelin, although the level of effect was less.

The sponsor did not believe that a Black Box warning in relation to bone loss is warranted in the Australian PI. The FDA required the Black Box warning in the US PI in 2005 when

the BMD decline was known but no good evidence had yet been generated that the BMD decline was reversible. Kaunitz et al (2006) and Harel et al (2010) showed that the 5% (average) decline in BMD is reversible in adults and also in adolescents.[26,27] Furthermore, fracture data from the UK General Practice Research Database (GPRD) were not available in 2005. That is, the basic premise of the black box is not that a 5% BMD decline is necessarily dangerous in and of itself (since that is what happens in a normal pregnancy and pregnancy history has not been shown to be a risk factor for osteoporosis) but that this BMD decline could translate into more fractures. A paper "Retrospective Cohort Study of DMPA and Fractures in Reproductive Age Women" presented by Kaunitz at the ARHP meeting in Atlanta 22 Sept. 2010 shows that DMPA use (mostly IM) has no effect on fracture incidence – that is, that DMPA does not increase fracture incidence in women who use it.[28] Women were followed for as long as 15 years (average was 6 years). There were 312,000 total in this retrospective GPRD cohort study (25% were DMPA users). The study showed that DMPA users have 40% more fractures than non-users but that they have this "higher" (although not 'increased') fracture rate before they even start using DMPA and their rate does not increase after they start using DMPA. Furthermore, a Black Box warning does not appear in the Australian PI for Depo-Provera.

5. Of note, a life table analysis of the Pearl Index1has not been done. Therefore the upper bound of the 95% CI has been deleted from the PI. The ACPM may have a view on this as the statistic is used by prescribers to make comparisons with other methods.

Since there were no contraceptive failures in the two pivotal contraception trials the sponsor did not perform a life table analysis. However, a simple calculation of the 95% CI for the proportion (zero events among the total number treated for one year) shows that the upper bound of the 95% CI is approximately equal to 0.3%. This would not represent the "observed" PEARL Index that prescribers would be accustomed to seeing, but does provide a statistical estimate of the upper bound for the contraceptive failure rate for the product.

6. The indication relating to endometriosis is based on one markedly underpowered study and one slightly underpowered study that at least show consistent trends. The Committee's advice is sought on the adequacy of the data to support efficacy. In women with endometriosis who are at risk of osteoporosis, danazol is probably a better choice than depot MPA or a GnRH agonist. Unfortunately, this has not been studied.

Danazol was not studied in our development program. The results of Studies 268 and 270 did suggest that Sayana is able to provide efficacy that is similar to that provided by leuprolide with significantly less adverse BMD effect. Therefore, we believe that Sayana is considered a reasonable treatment option for properly selected patients with endometriosis.

7. There are statistical issues with this application:

1. *The use of ITT and not PP analyses in non-inferiority studies;*
2. *The lack of a 95% upper limit of the CI in the Pearl Index; and,*
3. *The extensive analyses of underpowered studies in endometriosis when not even the primary endpoint could be reported.*

[26] Kaunitz AM, Miller PD, Montgomery Rice V, et al. Bone mineral density in women aged 25–35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. Contraception 2006; 74: 90-99.

[27] Harel Z, Cole Johnson CC, Gold MA, et al. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010; 81: 281-291.

[28] Kaunitz AM, Harel Z, Bone H et al. Retrospective Cohort Study of DMPA and Fractures in Reproductive Age Women. ARHP; Atlanta 22 Sept. 2010.

The issues related to the CI for the PEARL Index and the statistical power of the endometriosis studies have been addressed, briefly, in responses given above.

With respect to the use of ITT versus PP analyses, it should be noted that the analyses in these studies were, of course, done according to the prospectively defined plan. The analyses presented in the CSR included analyses in the Evaluable Patients population, but a PP population was not specifically pre-defined in the analysis plan. It could be possible to undertake such an analysis post hoc, but we would welcome input from TGA regarding the specific requirements for such an analysis before that work commences.

Conclusion

The sponsor supported the Delegate's recommendation to approve the application for a new dosage, new route of administration and new trade name for Depo-Provera suspension for injection that will be marketed as Sayana (medroxyprogesterone acetate) 104 mg/0.65 mL suspension for subcutaneous injection in a pre-filled syringe. Pfizer also believes that the subsequent published papers show that BMD decline is reversible and they support the exclusion of a black box warning in the Australian PI.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

Endometriosis: *Treatment of visually proven (by laparoscopy) endometriosis. Symptomatic control of endometriosis when surgery has been unsuccessful or is contraindicated.*
Contraception (ovulation suppression): *For long-term prevention of pregnancy in women when administered at 3-month intervals.*
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use Sayana long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (See PRECAUTIONS).

In making this recommendation, the ACPM considered that the currently available dose of medroxyprogesterone acetate (MPA - Depo-Provera) is 150 mg IM 12 weekly. Depo-Provera has been shown to be extremely effective at inducing ovarian suppression. Clear contraceptive efficacy was demonstrated in three studies. The two comparator trials with leuprolide in the treatment of endometriosis were both underpowered frustrating any real conclusions as to efficacy but suggested some efficacy but the response to treatment was significantly greater with leuprolide. On balance, Sayana is probably effective in the treatment of endometriosis given that C_{min} at 91 days is above the threshold for ovulation suppression and this is the basis for treatment of endometriosis.

Overall, the rate of adverse events of this subcutaneous preparation are consistent with those of the IM preparation and was similar for leuprolide but of different types. One of the risks of treatment long term is a potential decrease in bone density (BMD), however, there is some evidence for recovery after cessation of the drug. This risk needs to be clearly stated but a boxed warning was not considered necessary.

In addition to issues with BMD, the delay to fertility potential after cessation of Depo-MPA has been shown to be greater compared to leuprolide, although rates are similar by 24 months. Study 272 demonstrated Sayana and Depo-MPA treatment had similar delays to return of ovulation.

The ACPM, taking into account the submitted evidence of safety and efficacy, agreed with the Delegate that there is a favourable benefit-risk profile for this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sayana medroxyprogesterone acetate 104mg/0.65mL suspension for injection syringe, indicated for:

> ***Endometriosis:*** *For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra-indicated or has been unsuccessful.*
>
> ***Contraception (ovulation suppression):*** *For long-term prevention of pregnancy in women when administered at 3-month intervals.*
>
> *Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use Sayana long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see PRECAUTIONS).*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

SAYANA® (medroxyprogesterone acetate)
Suspension for Injection

NAME OF THE MEDICINE

Non-proprietary name: medroxyprogesterone acetate

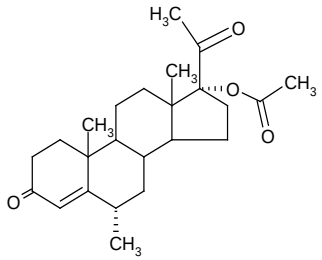
Chemical name: 6α-methyl-3,20-dioxopregn-4-en-17α -yl acetate

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

Molecular weight: 386.5

CAS Registry Number: 71-58-9

The structural formula of medroxyprogesterone acetate is shown below:



DESCRIPTION

Medroxyprogesterone acetate is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200º and 210ºC. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg medroxyprogesterone acetate in 0.65 mL suspension for injection.

Each pre-filled syringe contains the following inactive ingredients:
methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, sodium phosphate – monobasic, sodium phosphate – dibasic dodecahydrate , methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

PHARMACOLOGY

Mechanism of action

Medroxyprogesterone acetate is an analogue of 17 α-hydroxyprogesterone with anti-oestrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

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

Supression of serum oestradiol concentrations and a possible direct action of medroxyprogesterone acetate (MPA) on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Pharmacokinetics

The pharmacokinetic parameters of medroxyprogesterone acetate (MPA) following a single subcutaneous (SC) injection of MPA are shown in Table 1.

Table 1. Pharmacokinetic Parameters of MPA After a Single SC Injection of MPA 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.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. 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.

A direct bioequivalence study between the intramuscular formulation, Depo-Provera, and SAYANA, given subcutaneously at each of the two proposed sites has not been conducted.

Effect of Injection Site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (Cmin; 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 binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised 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) 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

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC 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 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.

Renal Impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic Impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see CONTRAINDICATIONS).

CLINICAL TRIALS

Contraception Studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the PEARL Index was 0.20 pregnancies per 100 women-years of use.

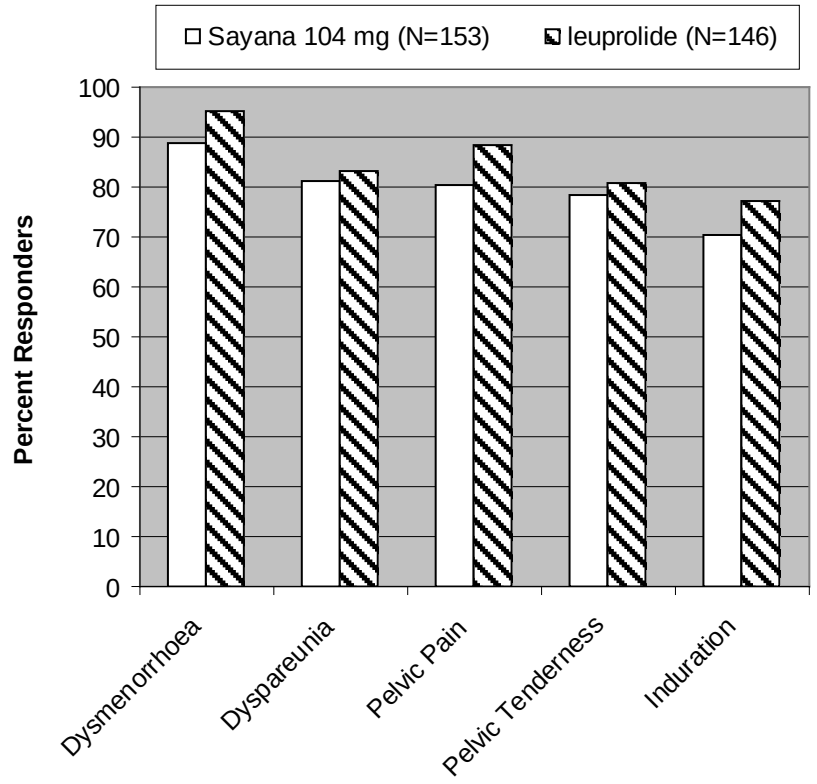
Endometriosis Studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomized, evaluator-blinded (single-blinded), multicenter, phase 3 efficacy and safety study comparing Sayana and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with Sayana (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of Sayana patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of Sayana to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 1).

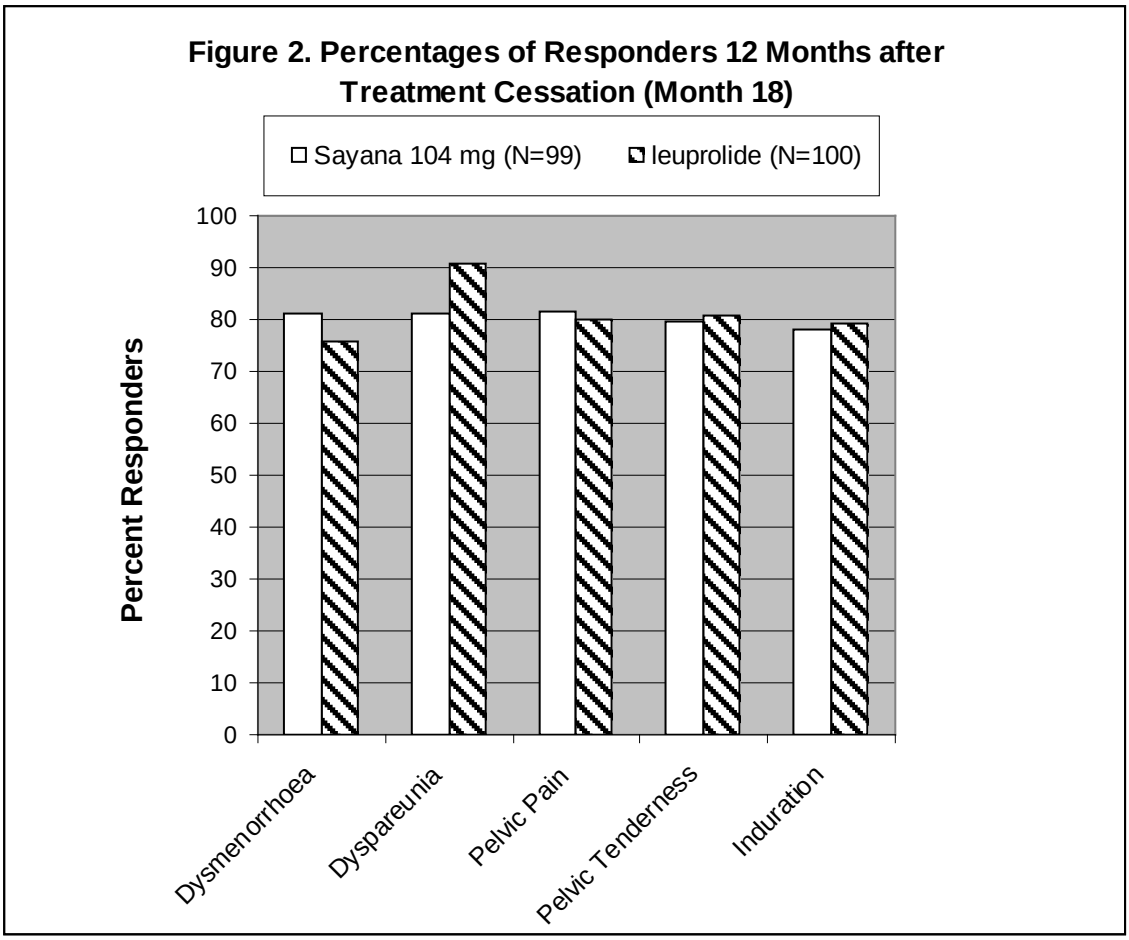
Figure 1. Percentages of Responders at End of Treatment (Month 6 or Last Assessment if Earlier)



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SAYANA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SAYANA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SAYANA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SAYANA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at month 3, and 29.0% at month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at month 3, and 71.2% at month 6. No pregnancies were reported during the 6-month active treatment period with either SAYANA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SAYANA - conception occurred at 72 days after injection.



Bone Mineral Density Changes in Adult Women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (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 use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using Depo-Provera Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 2.

Table 2. Mean Percent Change from Baseline in BMD in Adult Women Using SAYANA 104 mg for Contraception

	Time on Treatment	Lumbar Spine		Total Hip		Femoral Neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SAYANA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the Sayana women became pregnant while one of the Depo-Provera women became pregnant and was discontinued at 21 months.

BMD Changes in Adult Women after Six Months of Treatment for Endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 3).

Table 3. Mean Percent Change from Baseline in BMD: after 6 Months on Therapy with SC MPA or Leuprolide and 6 and 12 Months after Stopping Therapy

Time of Measurement	**Lumbar Spine**				**Total Hip**			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD Changes in Adolescent Females (12–18 years) after Long-Term Treatment for Contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed 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; 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, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that 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. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from DMPA use remains to be investigated.

INDICATIONS

Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra-indicated or has been unsuccessful.

Contraception (ovulation suppression): For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use SAYANA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see PRECAUTIONS).

CONTRAINDICATIONS

1. Known sensitivity to medroxyprogesterone acetate or any of the excipients - see DESCRIPTION Section for a list of ingredients.
2. Known or suspected pregnancy - See PRECAUTIONS, Use in Pregnancy
3. Known or suspected malignancy of the breast or genital organs
4. Undiagnosed vaginal bleeding
5. Severe hepatic impairment
6. Metabolic bone disease
7. Patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
8. Undiagnosed urinary tract bleeding
9. Undiagnosed breast pathology
10. Missed abortion

11. Severe uncontrolled hypertension

PRECAUTIONS

Route of Administration

SAYANA is not formulated for intramuscular injection. SAYANA must be given by subcutaneous injection.

Loss of Bone Mineral Density (BMD)

Use of SC MPA reduces serum oestrogen levels and is associated with significant loss of BMD due to the known effect of oestrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian oestrogen 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 SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

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.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to CLINICAL TRIALS section. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using MPA 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 4 for further details.

Table 4. 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.

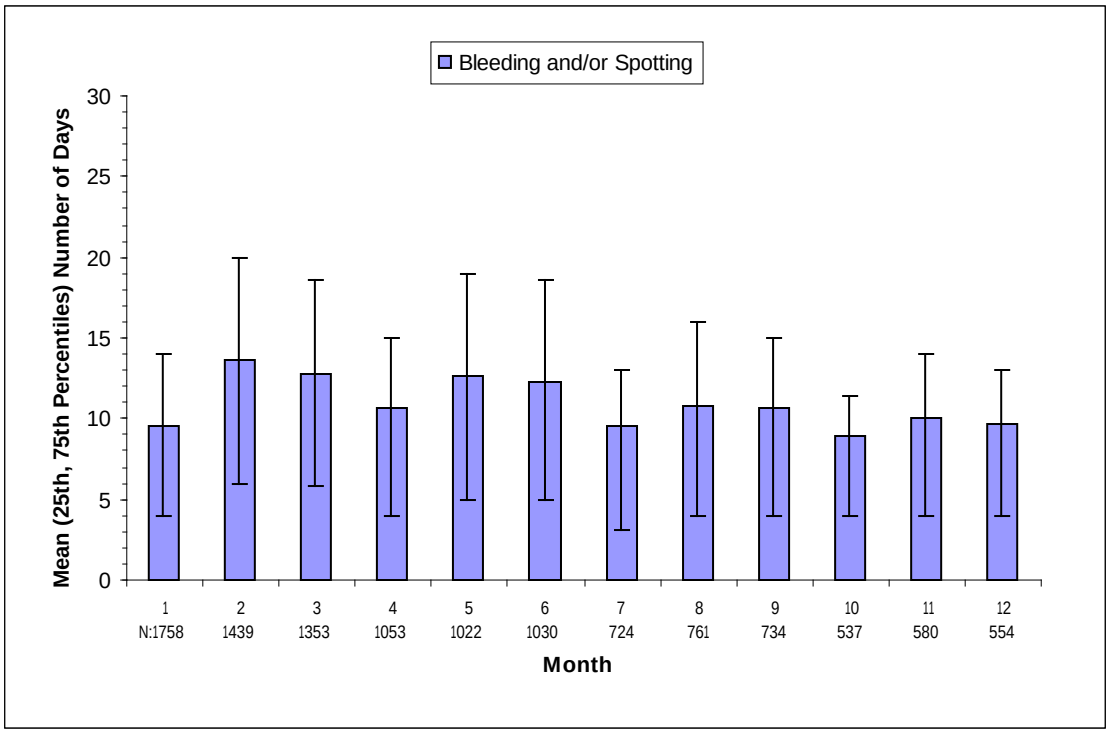
Bleeding Irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during month 6 and 56.5% experienced amenorrhoea during month twelve. .

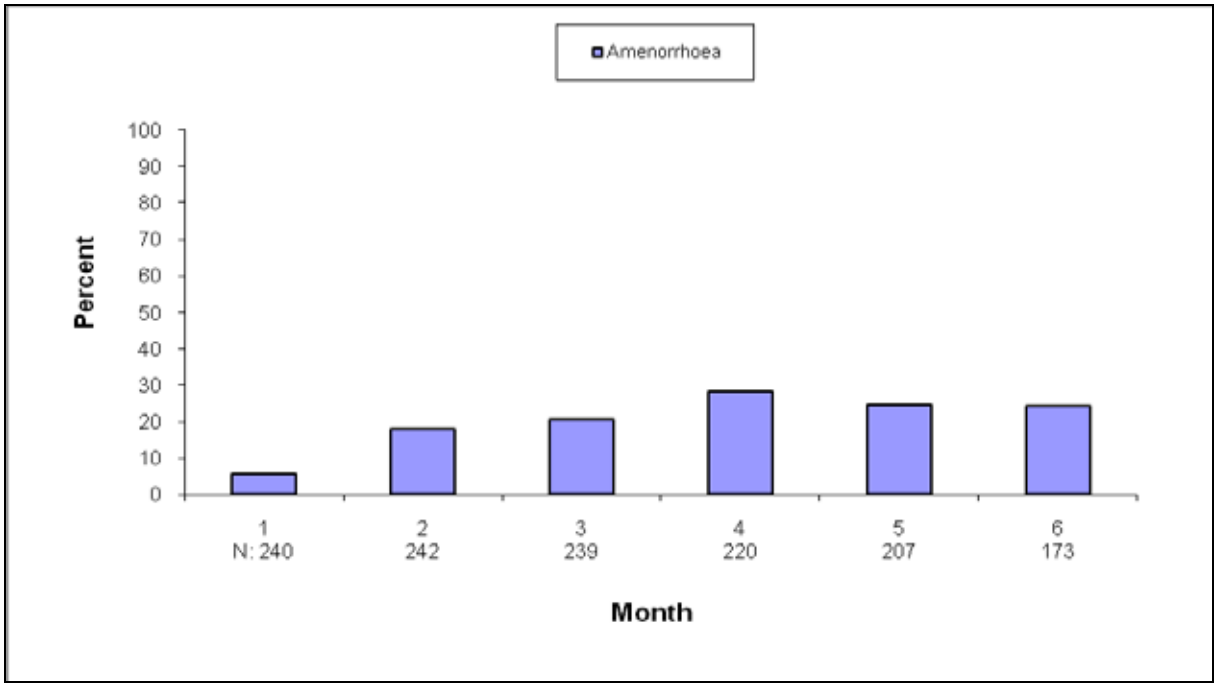
The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 3 and 4.

Figure 3. Mean (25th, 75th Percentiles) Number of Bleeding and/or Spotting Days in the Subgroup of Women with Bleeding and/or Spotting by Month for Women Treated with SC MPA 104 mg in Contraception Studies



N = Number of subjects with bleeding and/or spotting during indicated month

Figure 4. Percentages of SC MPA Treated Women with Amenorrhoea per 30-Day Month in Endometriosis Studies (Combined ITT Population, N=289)



N = Number of subjects in analysis for indicated month

Cancer Risks

Long-term case-controlled surveillance of depot medroxyprogesterone acetate (MPA) IM 150 mg use 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 in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of MPA IM use.

The overall relative risk of breast cancer associated with the use of MPA IM appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of MPA IM in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to MPA IM. The risk of breast cancer was comparable in similar groups of women who used either MPA IM or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A Relative Risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.
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 up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used MPA IM was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of MPA IM in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and Anaphylactoid Reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Physical Examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Ocular Disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic Disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, 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 SC MPA use in this population. (See CONTRAINDICATIONS)

Fluid Retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight Changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the 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.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for MPA-SC subjects was comparable to that of MPA-IM subjects.

Return of Ovulation

Following a single dose of SC MPA 104 mg, 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, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Protection Against Sexually Transmitted Diseases

Patients should be counselled that SC MPA does not protect against HIV infection (AIDS) or other sexually transmitted diseases. The patient should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

Depression

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

Injection Site Reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver Function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

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 may be affected by progestogen therapy:

(a) Plasma and urinary steroid levels are decreased (e.g. progesterone, oestradiol, pregnanediol, testosterone, cortisol).

(b) Plasma and urinary gonadotropin levels are decreased (e.g. LH, FSH).

(c) Sex-hormone-binding-globulin (SHBG) concentrations are decreased.

(d) T_3-uptake values may decrease.

(e) There may be small changes in coagulation factors.

(f) Sulfobromophthalein and other liver function test values may be increased slightly.

(g) There may be small changes in lipid profiles.

Use in Pregnancy - Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including medroxyprogesterone acetate . In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. 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.

Genotoxicity

Medroxyprogesterone acetate was negative in assays for bacterial Mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Accidental Pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after injection of medroxyprogesterone acetate Injection 150 mg IM may be at an increased risk of low birth weight. The attributable risk is 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.

Ectopic Pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in Lactation

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.

Paediatric Use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. **In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.** 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 (see CLINICAL TRIALS section). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

Use in the Elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Interactions with Other Medicines

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of medroxyprogesterone acetate. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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 metabolising enzymes.

Effects on Ability to Drive and Use of Machines

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

ADVERSE EFFECTS

In five clinical studies of MPA SC involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- Uterine bleeding irregularities (35%, n=75)
- Increased weight (18%, n=39)
- Decreased libido (11%, n=23)
- Acne (10%, n=21)
- Injection site reactions (6%, n=12)

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- Headache (9%)
- Intermenstrual bleeding (7%)
- Increased weight (6%)
- Amenorrhea (6%)
- Injection site reactions (5%)

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders: fatigue, injection site pain

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhea, nausea

Infections: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial

Investigations: abnormal cervix smear

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain

Nervous system disorders: dizziness, insomnia

Psychiatric disorders: anxiety, depression, irritability, decreased libido

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine hemorrhage, vaginal hemorrhage

Skin disorders: acne

Vascular disorders: hot flushes

The following events have been associated with the use of MPA SC for contraception:

MEDDRA SOC	**EVENT**
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight changes
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disturbance, libido decreased, mood disorder, hypersomnia, formication
Nervous system disorders	Headache, dizziness, migraine
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsuitism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle cramps, pain in limbs, polyarthralgia
Reproductive system and breast disorders	Amenorrhea, breast pain/tenderness, intermenstrual bleeding, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), irritability
Investigations	Abnormal liver enzymes, cervical smear abnormal

The following events have been associated with the use of MPA SC for endometriosis-associated pain:

MEDDRA SOC	EVENT
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight changes
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, mood disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in limbs, polyarthralgia
Reproductive system and breast disorders	Breast pain/tenderness, galactorrhoea, intermenstrual bleeding, menorrhagia, ovarian cyst, pelvic pain, uterine haemorrhage, vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on MPA SC use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by≥1% of patients in the MPA SC group (ITT population) is shown in the table below:

Adverse Event ++	DMPA-SC N = 153		Leuprolide N = 146	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

1. Anaphylaxis, anaphylactoid-like reactions, angioedema

2. Cardiovascular – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure

3. Central Nervous System – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders, confusion, euphoria, changes in libido, loss of concentration

4. Skin and mucous membranes - urticaria, pruritus, rash, acne, hirsutism, alopecia and sweating

5. Gastrointestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function, vomiting

6. Breast – mastodynia, tenderness, galactorrhoea

7. Cervix - changes in the position of the transformation zone and in secretions, cervical erosions

8. Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia, loss of bone mineral density

9. Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts

10. Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria

11. Genitourinary – prolonged anovulation

Please refer to the Depo-Provera product information for additional adverse events that have been noted with the intramuscular formulation.

Post marketing experience

The following reactions have been reported with Depo-Provera Contraceptive Injection and may occur with use of SC MPA:

General disorders: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst

Blood and lymphatic system disorders: anemia, blood dyscrasia

Cardiac disorders: tachycardia

Gastrointestinal disorders: gastrointestinal disturbances, rectal bleeding

Hepato-biliary disorders: jaundice

Immune system disorders: allergic reaction

Infections: genitourinary infections

Investigations: decreased glucose tolerance

Musculoskeletal, connective tissue, and bone disorders: loss of bone mineral density, scleroderma

Neoplasms: breast cancer, cervical cancer

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence

Psychiatric disorders: increased libido, nervousness

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, prolonged anovulation, unexpected pregnancy, uterine hyperplasia, vaginal cyst

Respiratory disorders: asthma, dyspnea, hoarseness

Skin disorders: angioedema, dry skin, increased body odor, melasma, pruritus, urticaria

Vascular disorders: deep vein thrombosis, pulmonary embolus, thrombophlebitis

In postmarketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

DOSAGE AND ADMINISTRATION

CONTRACEPTION AND ENDOMETRIOSIS INDICATIONS

Route of Administration

SAYANA must be given by subcutaneous injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA is not formulated for intramuscular injection.**

It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: prefilled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA

pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First Injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days post partum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and Subsequent Injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

IF USING FOR CONTRACEPTION AND SWITCHING FROM ANOTHER METHOD

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (oestrogen plus progestin) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from Depo-Provera IM (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for Depo-Provera IM (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

IF USING FOR TREATMENT OF ENDOMETRIOSIS

Treatment for longer than two years is not recommended, due to the impact of long-term SAYANA on bone mineral density. If symptoms return after discontinuation of treatment, bone mineral density should be evaluated prior to retreatment.

Children and Adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see CLINICAL TRIALS section and PRECAUTIONS section). 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.

Use in Renal Impairment

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Use in Hepatic Impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

OVERDOSAGE

No serious medical effects have been reported in association with overdosage of medroxyprogesterone acetate IM injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticord excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

Contact the Poisons Information Centre (13 11 26) for advice on the management of an overdose.

PRESENTATION

SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

STORAGE CONDITIONS

Store below 25°C. Do not freeze.

NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISONS SCHEDULE

Schedule 4

DATE OF APPROVAL

Approved by Therapeutic Goods Administation:

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #