

Long-acting reversible contraception: subcutaneous depot medroxyprogesterone acetate (DMPA-SC)

Evidence summary

Published: 28 January 2014

[nice.org.uk/guidance/esnm31](https://www.nice.org.uk/guidance/esnm31)

Key points from the evidence

The content of this evidence summary was up-to-date in January 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

A new formulation of depot medroxyprogesterone acetate (DMPA) for subcutaneous administration (DMPA-SC 104 mg/0.65 ml, Sayana Press) was shown to be as effective as DMPA given by intramuscular administration (DMPA-IM 150 mg/ml, Depo-Provera) for preventing pregnancy. Bone mineral density (BMD) loss and weight gain were similar with both methods of administration.

<p>Effectiveness</p> <ul style="list-style-type: none"> • The Pearl Index (number of pregnancies per 100 woman-years exposure) was 0 (3 studies including 3565, 5616 and 10,407 woman-cycles excluding months when barrier contraception was used or no intercourse occurred). • Contraceptive efficacy was maintained in women who were overweight or obese (6.3–25.1% of women in the studies had a BMI >30 kg/m²). 	<p>Safety</p> <ul style="list-style-type: none"> • Use of DMPA is associated with significant loss of BMD, which is greater with increasing duration of use, but BMD appears to increase after DMPA is stopped. • There was no significant difference between DMPA-IM and DMPA-SC in the decrease in BMD density after 3 years' use. • Weight gain is possible with DMPA-SC but there is wide variation between individual women.
<p>User factors</p> <ul style="list-style-type: none"> • Contraceptive efficacy does not depend on daily concordance. • Subcutaneous injection may be more acceptable than intramuscular administration to some women, including those at risk of haematoma due to bleeding disorders or anticoagulation. • The return to fertility (ovulation) may be delayed for up to 1 year after DMPA is stopped. 	<p>Resource implications</p> <ul style="list-style-type: none"> • The cost of each DMPA-SC injection is £6.90, administered every 13 weeks (±7 days). • The cost of each DMPA-IM injection is £6.01, administered every 12 weeks (±5 days).

Key points

Sayana Press is a formulation of DMPA for subcutaneous administration (DMPA-SC) for use as long-term female contraception, administered every 13 weeks. It is an alternative to DMPA administered by intramuscular injection (DMPA-IM, Depo-Provera) and was launched in the UK in June 2013. DMPA works by inhibiting gonadotrophin secretion, which, in turn, prevents ovulation.

This evidence summary is based on 3 trials that evaluated the contraceptive efficacy and safety of DMPA-SC. One of these was a randomised controlled trial that compared subcutaneous and

intramuscular administration of DMPA over 2 years with an optional 1-year extension, and also evaluated the effect of DMPA on BMD ([Kaunitz et al. 2009](#)); the other 2 studies were 1-year non-comparative studies ([Jain et al. 2004](#)).

The trials used DMPA-SC presented in a pre-filled syringe. The brand name for this product is Sayana, but Sayana was never marketed in the UK (Pfizer, personal communication, 2013). The [UK public assessment report for Sayana Press](#) (the same formulation of DMPA-SC as in Sayana but presented in a Uniject injection device) concluded that there was no clinically important difference in pharmacokinetics between the 2 presentations.

In all 3 studies, no pregnancies were recorded with DMPA-SC during use up to 3 years (a total of 19,588 woman-cycles excluding months when barrier contraception was used or no intercourse occurred). In the comparative trial, 1 woman in the DMPA-IM group became pregnant. Rates of decrease of BMD were not statistically significantly different in the DMPA-SC and DMPA-IM intervention groups after up to 3 years of use in the comparative trial; during this period, 55.6% (35/63) of DMPA-SC recipients and 51.9% (28/54) of DMPA-IM recipients had decreases of at least 5% in total hip BMD from baseline.

In the comparative trial, after 3 years' use, women in the DMPA-SC group had a mean (\pm [standard deviation](#)) weight gain of 4.5 ± 8.5 kg and women in the DMPA-IM group had a mean weight gain of 5.8 ± 8.7 kg. There were large individual variations in weight over 1 year, with some women losing and some women gaining more than 9 kg. The [summary of product characteristics \(SPC\) for Sayana Press](#) states that body weight was monitored for 12 months in phase III studies; 50% of women remained within 2.2 kg of their initial body weight, 12% of women lost more than 2.2 kg and 38% of women gained more than 2.3 kg.

The [SPC](#) advises that, because loss of BMD may occur in women of all ages who use DMPA-SC long term, a risk/benefit assessment should be considered, which also takes into consideration the decrease in BMD that occurs during pregnancy and lactation. In particular, in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered before use of DMPA-SC. In adolescents, use of DMPA-SC is indicated only when other contraceptive methods are considered unsuitable or unacceptable, because of unknown long-term effects of bone loss associated with DMPA-SC in the critical period of bone accretion. The [SPC](#) advises careful re-evaluation of the risks and benefits of use in women who wish to continue use for more than 2 years.

Limitations to the evidence for DMPA SC include the lack of comparisons with other contraceptive options and the high discontinuation rate in the study by [Kaunitz et al. \(2009\)](#). However, the [UK](#)

[public assessment report for Sayana](#) accepted that the studies provided sufficient evidence of contraceptive efficacy. This is because they were large enough that the calculated 2-sided 95% confidence interval for the overall Pearl Index (number of pregnancies per 100 woman-years) was sufficiently narrow (in accordance with the European Medicines Agency's [guideline on clinical investigation of steroid contraceptives in women](#)). The [UK public assessment report for Sayana Press](#) concluded that there was no clinically important difference in pharmacokinetics between Sayana and Sayana Press.

In addition, the 2 non-comparative studies lasted only 1 year and only 66 women in the study by [Kaunitz et al. \(2009\)](#) received DMPA-SC for 3 years. Thus, there is limited evidence of long-term safety data from clinical studies, although it is reasonable to expect that experience from long-term use of DMPA-IM is likely to give an indication of potential harms.

The NICE clinical guideline on [long-acting reversible contraception \(LARC\)](#) gives recommendations on the use of DMPA, and Sayana Press provides an alternative route of administration for DMPA from the intramuscular route, at a similar cost. A review of this product [from the Faculty of Sexual and Reproductive Healthcare \(FSRH\)](#) commented that DMPA-SC may be a preferable form of administration compared with intramuscular DMPA in women at risk of haematoma. The FSRH review also noted that it has potential for self-administration, although it is not licensed for this indication.

Local decision-makers will need to consider the evidence for DMPA-SC with that for DMPA-IM and other LARC methods. Factors relating to individual women, and the licensed indications, dosage intervals and costs of the various LARC methods will need to be taken into account in the context of [NICE guidance](#).

Key evidence

Kaunitz AM, Darney PD, Ross D et al. (2009). [Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density](#). *Contraception* 80: 7–17.

Jain J, Jakimiuk AJ, Bode FR et al. (2004). [Contraceptive efficacy and safety of DMPA-SC](#). *Contraception* 70: 269–275.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be

of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Relevance to NICE guidance programmes

Depot medroxyprogesterone acetate for subcutaneous administration (DMPA-SC) has not yet been considered through the topic selection process for NICE technology appraisals, and is not currently planned into any other work programme.

Introduction

NICE clinical guideline 30, [long-acting reversible contraception \(LARC\)](#), defined LARC as contraceptive methods that need administration less than once per cycle or month, including copper intrauterine devices (IUDs), progestogen-only intrauterine systems (IUS), progestogen-only injectable contraceptives and progestogen-only subdermal implants. Contraceptive vaginal rings were not included in the guideline because they were not licensed for use in the UK at the time of publication.

The [NICE guideline](#) states that increased use of LARC methods could help reduce rates of unintended pregnancy. In contrast to the oral contraceptive pill, LARC methods do not depend on daily concordance and have been shown to be a more cost-effective option. Intrauterine devices and implants were shown to be more cost effective than injectable contraceptives.

The [NICE guideline](#) estimated that about 30% of pregnancies are unplanned. The Department of Health's [Abortion statistics for 2012](#) indicate that age-standardised rate for legal abortions per 1000 female residents aged 15–44 years in England and Wales was 16.5, the lowest rate for 16 years. The rate of abortion was highest among women aged 21 years (31 per 1000).

The Health and Social Care Information Centre reported [information on NHS community contraceptive clinics in England](#) in 2012/13 (family planning clinics and clinics run by voluntary organisations such as Brook Advisory Centres; data on contraception obtained from GP practices or outpatient clinics were not reported). Use of LARC accounted for the primary methods of contraception among 30% of women who attended NHS community contraceptive clinics in England in 2012/13, of whom 30% chose injectable contraceptives (9% of all women attending).

The percentage of women choosing LARC as a primary method of contraception increased with age, from 18% of those under 15 years to 43% of women aged 35 years and over. However,

injectable contraceptives were most popular among women aged 16–24 years (chosen by 10–11% of women attending clinics); this option was chosen by fewer women aged under 15 years (6%) and 35 years and over (8%). The oral contraceptive pill was the most popular choice of contraception with 47% of women attending NHS community contraceptive clinics selecting this option; 20% of women reported using the male condom.

A formulation of DMPA for intramuscular administration (Depo-Provera) has been in use in the UK since 1991. This evidence summary describes Sayana Press, a new formulation of DMPA for subcutaneous administration.

Product overview

Drug action

Depot medroxyprogesterone acetate (DMPA) for subcutaneous administration (DMPA-SC) inhibits the secretion of gonadotrophins which, in turn, prevents follicular maturation and ovulation. The primary mechanism of ovulation suppression also results in endometrial thinning, and these actions produce its contraceptive effect (see the [Sayana Press summary of product characteristics](#)).

New therapeutic indication

DMPA-SC is indicated for use as long-term female contraception. Each subcutaneous injection provides contraception for at least 13 weeks (± 1 week). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to 1 year.

Course and cost

The dose of DMPA-SC given in the [Sayana Press summary of product characteristics](#) is 104 mg administered by subcutaneous injection within the first 5 days of the menstrual cycle or post-partum in women who are not breastfeeding (if the woman is breastfeeding, the injection should not be given before 6 weeks post-partum).

The injection should be repeated at 13-week intervals. If given within 7 days after the 13-week interval, no additional contraception is needed. If the injection is given more than 7 days after the 13-week interval, pregnancy must be excluded before the injection is repeated and additional contraceptive precautions must be taken.

The cost of each prefilled injector containing 104 mg/0.65 ml suspension is £6.90 (excluding VAT: [MIMs December 2013](#)).

Evidence review

The comparative evidence for efficacy comes from 1 [randomised controlled trial](#) (RCT) that evaluated contraceptive efficacy and effect on bone mineral density (BMD) of depot medroxyprogesterone acetate (DMPA) by subcutaneous administration (DMPA-SC) compared with DMPA by intramuscular injection (DMPA-IM; [Kaunitz et al. 2009](#)). In addition, 2 large non-comparative trials evaluated the contraceptive efficacy of DMPA-SC ([Jain et al. 2004](#)). The study by Kaunitz et al. commenced as a sub-study of one of the studies by Jain et al., but was conducted in a separate group of women.

All the studies used the same formulation of DMPA-SC as Sayana Press, but administration was via a prefilled syringe instead of the Uniject injection device in which Sayana Press is presented (Pfizer, personal communication, 2013). However, assessment by the Medicines and Healthcare products Regulatory Agency (MHRA) concluded that there were no clinically important differences in pharmacokinetics between the 2 presentations (see [Evidence strengths and limitations](#)).

Study 1: [Kaunitz et al. \(2009\)](#)

- Design: 2-year RCT conducted in the USA, Canada and Brazil. Allocation was [concealed](#). Investigators and evaluators were [blinded](#) to the allocated administration route; the study drugs were administered by independent practitioners.
- Population: 534 sexually active women aged 18–35 years (mean 26 years) with regular menstrual cycles. Their mean BMI was 26 kg/m² (range 15.6–54.0 kg/m²; 25.1% had a BMI >30 kg/m²). Among the exclusion criteria were use of oral contraceptives, contraceptive implants or hormone-medicated intrauterine devices in the previous 2 months or having had DMPA-IM administered in the 10 months before enrolment (contraceptive patches and rings were not in use at the time of study enrolment); a lumbar spine or femur BMD T-score of less than –1.0. Calcium, multivitamins and other mineral supplements were not included in the study protocol but were prohibited if they were part of the participants' normal daily regimen. A modified [intention-to-treat](#) population was used for the safety outcomes (all randomised participants who received at least 1 dose of study drug) and efficacy outcomes (all randomised participants who received at least 1 dose of study drug and made at least 1 clinic visit after receiving the first dose).

- **Intervention and comparison:** women were randomised to either DMPA-SC 104 mg or DMPA-IM 150 mg. Injections were given at the initial visit (within the first 5 days of the menstrual cycle) and every 91 days (± 7 days) thereafter. Participants who completed 2 years of DMPA exposure were given the opportunity to continue for a third year in the study either with the same DMPA formulation they had been receiving or without DMPA. Participants kept a diary to record menstrual bleeding pattern, incidences of vaginal intercourse and use of barrier contraception.
- **Outcomes:** the primary efficacy outcome was the treatment-failure cumulative pregnancy rate at 2 years; treatment failure was defined as a positive pregnancy test before the next scheduled contraceptive injection. The incidence of treatment-failure pregnancy was assessed for each intervention group by calculating the rate and 95% confidence interval using the life-table method and the Pearl Index (defined as the number of pregnancies per 100 women-years of exposure). The primary safety outcome was the percentage change from baseline to 2 years in BMD at the total hip and lumbar spine. Lumbar spine (L1 to L4) and total hip BMD were evaluated by dual-energy X-ray absorptiometry (DXA) at the screening visit for baseline data and at the end of 1, 2 and 3 years' use.

Baseline demographics and bleeding-cycle histories were similar between the DMPA-SC and DMPA-IM groups. At each point when study drugs were administered, 92–100% of women received injections according to the specified time schedule. Few women in either study group ($\leq 5.2\%$) reported use of calcium supplements, and no participant reported bisphosphonate or chronic corticosteroid use.

Table 1 Summary of the comparative RCT data: [Kaunitz et al. \(2009\)](#)

	DMPA-SC	DMPA-IM	Analysis
Randomised	n=267	n=268	
Efficacy ^a	n=263	n=265	
Primary efficacy outcome: treatment-failure cumulative pregnancy rate after 2 years ^b	4344 women-cycles	4281 women-cycles	
Life-table method	0%	0.8%, 95% CI 0.00 to 2.37	not reported
Pearl Index ^c	0	0.28, 95% CI 0.00 to 0.83	not reported

Selected secondary efficacy outcome: adjusted treatment-failure cumulative pregnancy rate ^d , after 2 years	3565 woman-cycles	3442 woman-cycles	
Life-table method	0%	0.75%, 95% CI not reported	not reported
Pearl Index ^c	0	0.35, 95% CI not reported	not reported
Safety ^e	n=263	n=266	
Primary safety outcome: median percentage change in BMD after 2 years ^f :	-3.3%	-3.6%	p≥0.05
Total hip	-4.3%	-5.0%	p≥0.05
Lumbar spine			
Selected secondary safety outcomes			
Women showing at least 5% decrease in BMD after 1 year:	7.8% (13/166)	12.3% (20/162)	NS
Total hip	20.5% (34/166)	24.7% (40/162)	NS
Lumbar spine			
Women showing at least 5% decrease in BMD after 3 years:	55.6% (35/63)	51.9% (28/54)	NS
Total hip	58.1% (36/62)	39.6% (21/53)	NS
Lumbar spine			
Women reporting serious adverse events	3.8% (10/263)	2.3% (6/266)	NS
Women reporting any adverse event	81.4% (214/263)	77.8% (207/266)	not reported
Percentage of women with amenorrhoea:			
after 1 years' use	64.1% (100/156)	61.1% (91/149)	not reported
after 2 years' use	71.0% (66/93)	80.0% (68/85)	not reported

Weight gain	12.5% (33/263)	14.7%(39/266)	not reported
Injection site reaction	8% (21/263)	0.4% (1/266)	not reported

Abbreviations: BMD, bone mineral density; CI, confidence interval; DMPA-IM, depot medroxyprogesterone acetate by intramuscular injection; DMPA-SC, depot medroxyprogesterone acetate by subcutaneous administration; NS, reported as no statistically significant difference between intervention groups with no p value stated.

^a All randomised participants who received at least 1 dose of study drug and made at least 1 clinic visit after receiving the first dose.

^b Including months when barrier contraception was used at least sometimes or no intercourse occurred.

^c Defined as the number of pregnancies per 100 woman-years exposure.

^d Excluding months when barrier contraception was used or no intercourse occurred.

^e All randomised participants who received at least 1 dose of study drug: 1 woman randomised to DMPA-SC did not receive it and data were not available for 3 other women in the DMPA-SC group and 2 women in the DMPA-IM group.

^f Percentage change from baseline to year 2 in BMD at the total hip and lumbar spine (L1 to L4) measured by dual-energy X-ray absorptiometry (DXA) scan.

Studies 2 and 3: Jain et al. (2004)

The 2 non-comparative studies had the same design.

- Design: 1-year open-label, non-comparator, multicentre trials in the USA, Canada, Mexico, Peru, Brazil and Chile (study 2); and Russia, Bulgaria, Estonia, Latvia, Lithuania, Poland, Romania, Norway, United Kingdom, Indonesia and Pakistan (study 3).
- Population: Sexually active women aged 18–49 years (mean 28 years in study 2 and 32 years in study 3) with regular menstrual cycles. The mean BMI in study 2 was 25.3 kg/m² (range 14.7–57.7 kg/m²; 17.5% had a BMI >30 kg/m²), and in study 3 it was 23.2 kg/m² (range 15.4–40.6 kg/m²; 6.3% had a BMI >30 kg/m²). Among the exclusion criteria were use of oral contraceptives, contraceptive implants or hormone-medicated intrauterine devices in the previous 2 months or having had DMPA-IM administered in the 10 months before enrolment. A modified intention-to-treat population was used for the safety outcomes (all randomised participants who received at least 1 dose of study drug) and efficacy outcomes (all randomised

participants who received at least 1 dose of study drug and made at least 1 clinic visit after receiving the first dose).

- **Intervention:** DMPA-SC (104 mg/0.65 ml) was administered by subcutaneous injection into the anterior thigh or abdominal wall. Injections were given at the initial visit (within the first 5 days of the menstrual cycle) and every 91 days (± 7 days) thereafter for 1 year.
- **Outcomes:** the primary efficacy outcome was the treatment-failure cumulative pregnancy rate after 1 year; treatment failure was defined as a positive pregnancy test before the next scheduled contraceptive injection. The incidence of treatment-failure pregnancy was assessed for each intervention group by calculating the rate and 95% confidence interval using the life-table method and the Pearl Index. Secondary outcomes included changes to menstrual bleeding pattern and weight changes.

Compliance with the administration schedule was high; 95–97% of injections in study 2 and 92–96% of injections in study 3 were administered according to the specified time schedule.

Table 2 Summary of the non-comparative trials (Jain et al. 2004)

	Study 2: Americas trial (study in North and South America)	Study 3: Europe/Asia trial (study in Europe, Indonesia and Pakistan)
Randomised	n=722	n=1065
Efficacy ^a	n=720	n=1059
Primary outcome: treatment-failure cumulative pregnancy rate after 1 year ^b	7209 women-cycles	11,472 women-cycles
Life-table method	0%	0%
Pearl Index ^c	0	0
Selected secondary efficacy outcome: adjusted treatment-failure cumulative pregnancy rate ^d , after 1 year	5616 women-cycles	10,407 women-cycles
Life-table method	0%	0%
Pearl Index ^c	0, 95% CI not reported	0, 95% CI not reported
Safety		

Women reporting serious adverse events	1.3% (9/720)	1.4% (15/1060)
Total discontinuations due to adverse events	13.9% (100/720)	5.3% (56/1060)
Discontinuations due to increased or irregular vaginal bleeding	4% (29/720)	2.9% (31/1060)
Proportion with weight increase	8.2% (59/722)	4.2% (45/1065)
Mean weight change (\pm SD)	1.7 \pm 4.5 kg (n=487)	1.4 \pm 3.6 kg (n=856)
<p>Abbreviations: CI, confidence interval; SD, standard deviation.</p> <p>^a All randomised participants who received at least 1 dose of study drug and made at least 1 clinic visit after receiving the first dose.</p> <p>^b Including months when barrier contraception was used at least sometimes or no intercourse occurred.</p> <p>^c Defined as the number of pregnancies per 100 woman-years exposure.</p> <p>^d Excluding months when barrier contraception was used or no intercourse occurred.</p>		

Clinical effectiveness

After 2 years' use (primary outcome), [Kaunitz et al. \(2009\)](#) reported that there was 1 pregnancy in 4281 woman-cycles of exposure in the DMPA-IM group (cumulative failure rate [life-table method] 0.75%, Pearl Index 0.28), and no pregnancies in 4344 woman-cycles of exposure in the DMPA-SC intervention group (cumulative treatment failure rate [life-table method] 0%, Pearl Index 0). Similar results were reported when the months in which barrier contraception was used or no intercourse occurred were excluded from the analysis (3442 woman-cycles in the DMPA-IM group and 3565 woman-cycles in the DMPA-SC group). No further pregnancies were reported in the 1-year extension period (that is, in the third year of use), although it should be noted that these are effectively observational data because of the optional nature of the extension.

[Jain et al. \(2004\)](#) reported results for pregnancy prevention after 1 year from the 2 non-comparative trials. These trials also reported no pregnancies following a combined total of 18,681 women-cycles of exposure over the course of 1 year (16,023 woman cycles when the months in which barrier contraception was used or no intercourse occurred were excluded). The cumulative treatment failure rate (life-table method) was 0% and the Pearl Index was 0. The authors commented that the contraceptive efficacy of DMPA-SC was maintained in women who were overweight or obese.

Safety

Change in bone mineral density

The [Sayana Press summary of product characteristics](#) (SPC) states that use of DMPA-SC reduces serum oestrogen levels and is associated with significant loss of BMD because of the known effect of oestrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use; however, BMD appears to increase even after DMPA-SC is stopped and ovarian oestrogen production increases.

The [SPC](#) also states that a retrospective cohort study using data from the General Practice Research Database (GPRD) reported that women using DMPA have a higher risk of fracture compared with contraceptive users with no recorded use of DMPA (incident rate ratio 1.41, 95% confidence interval 1.35 to 1.47 for the 5-year follow-up period). The [SPC](#) states that it is not known if this is because of DMPA or other related lifestyle factors that have a bearing on fracture rate. It goes on to state that, in women using DMPA, the fracture risk before and after starting DMPA was not increased (relative risk 1.08, 95% confidence interval 0.92 to 1.26). The study could not determine whether use of DMPA has an effect on fracture rate later in life.

Change in BMD was the primary safety outcome in the study by [Kaunitz et al. \(2009\)](#). The authors reported that decreases in BMD were noted in both intervention groups over the course of the trial and the extension period up to 3 years. There were no significant differences between study groups in BMD except after 1 year of use, when the median decrease in lumbar spine BMD was statistically significantly greater in DMPA-IM recipients than in DMPA-SC recipients (-3.4% compared with -2.4%, $p=0.021$). However, the proportion of women with a reduction in BMD from baseline of 5% or more was not statistically significantly different at any time. At year 3, 8.1% and 5.6% of women in the DMPA-SC and DMPA-IM groups respectively, showed a decrease in total hip BMD T-score to a value below -1.0, whereas the corresponding proportions for the lumbar spine were 14.5% and 19.2%. No clinical osteoporotic fractures were reported during the trial.

Menstrual disturbance

In both study groups in the study by [Kaunitz et al. \(2009\)](#), irregular bleeding decreased with time, whereas the frequency of amenorrhea increased. Among women experiencing bleeding or spotting after 3 months of DMPA use, 33–40% had amenorrhea in the month after the second injection. After 1 year of use, 64% of women in the DMPA-SC group and 61% of women in the DMPA-IM group had amenorrhea, increasing to 71% and 80% respectively after 2 years of exposure. Intermenstrual bleeding was an adverse event in about 6% of women in both study groups.

[Jain et al. \(2004\)](#) reported that 55% of women had amenorrhoea after 12 months of use in a combined analysis of data from the non-comparative studies. In these trials, intermenstrual bleeding was reported in 6–8% of women. Increased or irregular vaginal bleeding were the most common side effects that led to women leaving the studies and occurred in 4% (29/720) of women in the Americas trial (study 2) and 2.9% (31/1060) in the Europe/Asia trial (study 3).

Weight gain

[Westhoff et al. \(2007\)](#) published analyses of data on weight gain from all 3 studies. In the non-comparative studies ([Jain et al. 2004](#)), mean (\pm standard deviation [SD]) weight gains of 1.7 kg (± 4.5 kg) and 1.4 kg (± 3.6 kg) were reported in the Americas trial (study 2) and the Europe/Asia trial (study 3) respectively after 1 year of use. In the comparative trial ([Kaunitz et al. 2009](#)), after 3 years' use women in the DMPA-SC group had a mean (\pm SD) weight gain of 4.5 ± 8.5 kg and women in the DMPA-IM group had a mean weight gain of 5.8 ± 8.7 kg.

[Westhoff et al. \(2007\)](#) commented that although overall increases in weight were seen in these studies, there were large individual variations in weight over 1 year, with some women losing and some women gaining more than 9 kg. Weight gain was a reason for stopping DMPA that was given by women in all trials: 5.7% (15/263) of all women in the comparative trial (study 1) and 2.5% (18/722) and 0.7% (7/1060) of women in the Americas trial (study 2) and the Europe/Asia trial (study 3).

Overall, no consistent differences in the distribution of weight change from baseline were observed by age group and there were no statistically significant differences in median weight gain between BMI subgroups in any study. The [SPC for Sayana Press](#) states that body weight was monitored for 12 months in phase III studies; 50% of women remained within 2.2 kg of their initial body weight, 12% of women lost more than 2.2 kg and 38% of women gained more than 2.3 kg.

Injection-site reactions

In the comparative study ([Kaunitz et al. 2009](#)), more injection-site reactions (which were all mild to moderate in severity) were observed in the DMPA-SC group (8%) than in the DMPA-IM group (0.4%) but the statistical significance of this difference was not reported. In the non-comparative trials ([Jain et al. 2004](#)), injection-site reactions were reported in 9.7% of women in the Americas trial (study 2) and 1.6% of women (31/1060) in the Europe/Asia trial (study 3).

Serious adverse events

[Kaunitz et al. \(2009\)](#) reported that there was no statistically significant difference between the intervention groups for the incidence of serious adverse events (3.8% of the DMPA-SC group and 2.3% of the DMPA-IM group). None of the serious adverse events were considered related to study drugs, with the exception of the single unintended pregnancy in the DMPA-IM group. [Jain et al. \(2004\)](#) reported serious adverse events in 1.3% (9/720) of women in the Americas trial (study 2) and in 1.4% (15/1060) of women in the Europe/Asia trial (study 3). Four of the serious adverse events in the Europe/Asia trial were considered to be drug related: uterine haemorrhage needing surgery in 2 women, menometrorrhagia needing surgery in 1 woman, and increased weight, difficulty in walking and limb pain in 1 woman.

Evidence strengths and limitations

A limitation to the evidence for DMPA-SC is the lack of comparisons with other current contraceptive options; use of a comparator is generally a minimum requirement for trials of drug efficacy. DMPA-SC was compared only with another formulation and administration route of DMPA in the study by [Kaunitz et al. \(2009\)](#), and the 2 studies reported by [Jain et al. \(2004\)](#) were non-comparative. Moreover, [Kaunitz et al. \(2009\)](#) reported high discontinuation rates of 56% and 59% of women receiving subcutaneous and intramuscular DMPA respectively, within the initial 2 years of the study.

However, in its [guideline on clinical investigation of steroid contraceptives in women](#), the European Medicines Agency states that non-comparative studies are acceptable for a new administration form as long as they are at least large enough to give the overall Pearl Index (number of pregnancies per 100 woman-years) with a 2-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (1 pregnancy per 100 woman-years).

The [UK public assessment report for Sayana](#) (DMPA-SC presented in a prefilled syringe) concluded that there were no pregnancies due to treatment failure in phase III studies of the product, which included 17,528 woman-cycles excluding months when intercourse did not take place or a barrier method was used. The calculated upper limit of a 95% confidence interval for the Pearl Index was 0.27; because this was much less than 1, the studies were accepted as providing sufficient evidence of contraceptive efficacy. Sayana was never marketed in the UK (Pfizer, personal communication, 2013). The [UK public assessment report for Sayana Press](#) (the same formulation of DMPA-SC as in Sayana but presented in a Uniject injection device) concluded that there was no clinically important difference in pharmacokinetics between the 2 presentations.

A further limitation of the study by [Kaunitz et al. \(2009\)](#) was that the group sizes were designed to detect a statistically significant difference if one existed in BMD measurements between groups – not to assess the more clinically relevant outcome of fracture incidence.

Finally, the 2 non-comparative studies lasted only 1 year and only 66 women in the study by [Kaunitz et al. \(2009\)](#) received DMPA-SC for 3 years. Thus, there is limited evidence of long-term safety data from clinical studies, although it is reasonable to expect that experience from long-term use of DMPA-IM is likely to give an indication of potential harms.

Context

Alternative contraceptives

The NICE clinical guideline on [long-acting reversible contraception \(LARC\)](#) offers information on the assessment and choice of LARC methods for different groups of women. Long-acting reversible hormonal contraception methods include depot medroxyprogesterone acetate (DMPA) by intramuscular (IM) or subcutaneous (SC) administration, the etonogestrel subdermal implant (Nexplanon), norethisterone enantate intramuscular injection (Noristerat) and the progestogen-only intrauterine system (Mirena). Copper-containing (non-hormonal) intrauterine devices are also available.

Costs of alternative contraceptives

Table 3 Costs of alternative long-acting reversible hormonal contraception methods

	Usual dose and duration of action	Unit cost excluding VAT
DMPA-IM (Depo-Provera)	150 mg/ml intramuscular injection every 12 weeks (± 5 days)	£6.01 ^a
DMPA-SC (Sayana Press)	104 mg/0.65 ml subcutaneous injection every 13 weeks (± 7 days)	£6.90 ^b
Etonogestrel implant (Nexplanon)	68 mg subdermal implant for up to 3 years	£79.46 ^b

Levonorgestrel intrauterine system (Mirena)	52 mg T-shaped intrauterine system (releasing approximately 20 microgram/24 hours) for up to 5 years	£88.00 ^b
Norethisterone enantate (Noristerat)	200 mg in 1 ml oily solution for intramuscular injection: may be repeated once after 8 weeks	£4.05 ^b
Abbreviations: DMPA-IM, depot medroxyprogesterone acetate by intramuscular injection; DMPA-SC, depot medroxyprogesterone acetate by subcutaneous administration. ^a Costs taken from Drug Tariff , December 2013 ^b Costs taken from MIMS , December 2013		

Estimated impact for the NHS

Likely place in therapy

The place in therapy of subcutaneous depot medroxyprogesterone acetate (DMPA-SC) is likely to be as an alternative choice of administration method and route for DMPA.

A recent review of this product [from the Faculty of Sexual and Reproductive Healthcare \(FSRH\)](#) commented that DMPA-SC may be a preferable form of administration compared with intramuscular DMPA in women at risk of haematoma due to bleeding disorders or anticoagulation. The FSRH review also noted that it also has potential for self-administration, although it is not licensed for this indication.

The [Sayana Press summary of product characteristics](#) states that, because loss of bone mineral density (BMD) may occur in females of all ages who use DMPA-SC long term, a risk/benefit assessment should be considered, which also takes into consideration the decrease in BMD that occurs during pregnancy and lactation. In particular, in women with significant lifestyle or medical risk factors for osteoporosis, other methods of contraception should be considered before using DMPA-SC. Significant risk factors for osteoporosis include:

- Alcohol abuse and/or tobacco use
- Chronic use of drugs that can reduce bone mass, such as anticonvulsants or corticosteroids
- Low BMI or eating disorder, such as anorexia nervosa or bulimia
- Previous low trauma fracture

- Family history of osteoporosis

In adolescents, use of DMPA-SC is indicated only when other contraceptive methods are considered unsuitable or unacceptable, because of unknown long-term effects of bone loss associated with DMPA-SC in the critical period of bone accretion.

Estimated usage

The available data for usage of DMPA are based on prescribing analysis of the formulation for intramuscular administration. According to manufacturer estimates and extrapolation from prescribing data, about 227,000 woman-years of use was prescribed in primary care (such as GP practices) in England in 2012 (Pfizer, personal communication, 2013). In addition, in 2012/13, 83,900 women attending NHS contraceptive clinics in England (family planning clinics and clinics run by voluntary organisations such as Brook Advisory Centres) used injectable contraception ([Health and Social Care Information Centre data](#)); it might be that some women obtained their contraception from both sources.

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Changes after publication

February 2014: Minor maintenance

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

For information about the process used to develop this evidence summary, see the [Evidence Summaries: new medicines integrated process statement](#).

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ISBN: 978-1-4731-0407-5