Medicines Adverse Reactions Committee

Meeting date	**8 March 2018**	Agenda item	3.2.3
Title	**Medroxyprogesterone and withdrawal syndrome**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Medroxyprogesterone	**Medicines** Depo-Provera, injection depot	**Sponsors** Pfizer NZ Ltd	
Funding	Yes		
Previous MARC meetings	Withdrawal syndrome/withdrawal symptoms and Depo-Provera have not been discussed previously.		
Schedule	Prescription medicine		
Advice sought	**The Committee is asked to advise whether:** – You would classify the problems that these women have experienced as withdrawal symptoms? – Any information regarding withdrawal symptoms should be included in the data sheet? – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

The Centre for Adverse Reactions Monitoring (CARM) recently received a case report describing withdrawal symptoms after stopping medroxyprogesterone acetate, MPA (brand name Depo-Provera).

The reported withdrawal symptoms included: feeling of having a viral infection with fatigue, eye pain, visual disturbance, itching, restlessness, agitation, shaking, nausea and shortness of breath. The reporter refers to internet forums where other women report the same symptoms on stopping Depo-Provera.

There is very limited information on this issue in medical literature. This may partly be because it is difficult to identify relevant studies. However, there are many reports in blogs and on discussion forums from women having problems like weight gain, hot flashes, painful breasts, sleeping problems, headaches, flu symptoms and nausea when discontinuing Depo-Provera.

Considering that this could be a problem for many women despite limited medical evidence, Medsafe considers that this safety concern be reviewed by the Committee.

2.0 BACKGROUND

2.1.1 Depo-Provera (medroxyprogesterone)

Depo-Provera (DMPA) is a progestin (a synthetic form of progesterone) indicated for contraception, treatment of endometriosis, adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma and treatment of hormonally-dependent recurrent breast cancer in post-menopausal women. The recommended dose for contraception is 150 mg every 3 months, administered by deep intramuscular injection. Depo-Provera is a long-acting progestin and the long duration of action is a result of a slow absorption from the injection site.

2.1.2 Effects of Depo-Provera

The text in this section is from the medical library UpToDate (1) unless otherwise specified.

The primary mechanism of action for Depo-Provera is to inhibit the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation. The inhibition of ovarian function results in a hypoestrogenic state, which results in endometrial thinning and renders the endometrium less receptive to implantation. In addition cervical mucus thickens, making sperm penetration of the cervix more difficult.

Following a single intramuscular dose of DMPA, the drug level in blood increases for approximately three weeks, reaching a peak concentration of up to 7 ng/mL for a few days. The level then declines until it becomes undetectable between 120 and 200 days following injection. There is considerable inter-individual variability in serum levels. Ovulation resumes at DMPA levels <0.1 ng/mL. After a 150 mg injection, ovulation does not occur for at least 14 weeks.

Serum progesterone levels are low (<0.4 ng/mL) for several months following an injection of DMPA since ovulation is suppressed. Estrogen levels vary, but most women have lower levels than normally cycling women.

Although DMPA does not permanently impact endocrine function, return of fertility may be delayed. Within 10 months of the last injection, 50 percent of women who discontinue DMPA to become pregnant will conceive; in a small proportion of women, however, fertility is not re-established until 18 months after the last injection. The persistence of ovulation suppression following DMPA discontinuation is not related to the duration of use. Women with lower body weights conceive sooner after discontinuing DMPA than women with higher body weights.

2.1.3 Adverse effects of Depo-Provera

Menstrual changes occur in all women using DMPA and are the most frequent reason for discontinuation. During the first months of use, episodes of unpredictable bleeding and spotting lasting seven days or longer are common (1).

Known adverse effects of Depo-Provera of interest for this paper are for example pelvic pain, breast tenderness, depression, insomnia, nervousness, anorgasmia, changes in libido, loss of concentration, somnolence, hot flush, abdominal pain, back pain and increased weight (2).

Adverse effects associated with DMPA use were illustrated in a clinical trial in which over 3900 DMPA users were followed for up to seven years. The following adverse effects were reported by more than 5% of subjects: menstrual irregularities (unscheduled bleeding or amenorrhea), weight changes, headache, abdominal pain or discomfort, nervousness, dizziness, and asthenia. Adverse reactions reported by 1% to 5% of subjects were for example decreased libido or anorgasmia, vaginitis, backache, pelvic pain, leg cramps, breast pain, depression, insomnia and hot flushes. This data is also included in the NZ data sheet.

A primary concern regarding the safety of long-term use of DMPA is the effect on bone density. One of the contraceptive actions of DMPA results from suppression of gonadotropin secretion, which in turn suppresses ovarian estradiol production. In hypoestrogenic states, bone resorption exceeds bone formation, resulting in a decline in bone mineral density (BMD) (1).

Observational studies have not reported any consistent effects of DMPA on mood (see also section 3.1). Progestins may cause or exacerbate depressive symptoms in certain subpopulations of women, including those with a history of premenstrual syndrome (PMS) or mood disorders (1).

The Cochrane institute has recently released an analysis of PMS and treatment with estrogen, where the PMS syndrome is described as a psychological and somatic disorder of unknown aetiology, with symptoms including breast tenderness, bloatedness, headaches, and muscle aches. Frequently reported emotional and behavioural symptoms include irritability, emotionality, low mood, oversensitivity, poor concentration and tiredness. PMS symptoms recur during the luteal phase of the menstrual cycle and disappear at the onset of menstruation. PMS is probably related to ovulation and may be due to ovarian steroid interactions relating to neurotransmittor dysfunction (3).

Comments: Many symptoms described in social media by women who have discontinued Depo-Provera resembles known adverse effects of Depo-Provera. The balance in the body of certain hormones changes both when starting and stopping treatment.

2.2 Withdrawal symptoms

A drug withdrawal syndrome is generally used to describe a variety of symptoms that may occur after the discontinuation of the medicine. Withdrawal symptoms can include for example increased sensitivity to pain, irritability, emotional instability, anxiety and depression, restlessness or insomnia, sweating, hot flashes, flu-like symptoms: weakness, body aches and headache or lack of/increased appetite (4).

Withdrawal symptoms are closely related to the addictive potential of a medicine.
The evaluation of drug withdrawal syndromes is difficult. Symptoms resulting from discontinuation of a medication may need to be distinguished from reappearance of disease symptoms or a "catching up" of the basic disease state, which may emerge in the absence of the pharmacological action of the drug (5). In some cases withdrawal syndrome might be better described as a discontinuation syndrome.

2.3 Data sheets

2.3.1 New Zealand

The data sheet for Depo Provera was revised 6 October 2017. Section 4.4 Special warnings and precautions for use states:

- Most women using DEPO-PROVERA experience disruption of menstrual bleeding patterns following the administration of either a single or multiple doses of MPA. With longer use fewer women experience irregular bleeding and more experience amenorrhoea. Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.
- Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life. Bone loss may be greater with increasing duration of use and may not be completely reversible in some women.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving DEPO-PROVERA therapy and the drug discontinued if the depression recurs to a serious degree.

Section 4.8 Undesirable effects lists for example breast pain, breast tenderness, depression, insomnia, nervousness, anorgasmia, changes in libido, confusion, euphoria, headache, loss of concentration, somnolence, fine-hand tremors and sweating as adverse effects reported for Depo-Provera.

The data sheet includes data from several studies when women have been followed after stopping Depo-Provera, but in the aspect of measuring effect on bone density. Withdrawal syndrome or withdrawal symptoms are not currently included in the data sheet or in the CMI.

The product information for Depo-Provera in the UK states that patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on Depo-Provera therapy.

Comments: In the data sheet for Depo-Provera, the adverse effects are not listed by frequency. Withdrawal syndrome or withdrawal symptoms are not currently included in the data sheet or in the CMI.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

There is little published scientific evidence on symptoms post Depo-Provera beyond research about bone density and length of time to return to fertility. Two publications have been found regarding DMPA and potential effects on mood.

3.1.1 Civik D, Scholes D, Ichikawa L et al, 2000 (6)]

A population-based prospective study to evaluate the possible effects of depot medroxy-progesterone acetate (DMPA) injectable contraception on depressive symptoms included women aged 18-39 years old enrolled at a health maintenance organization. At baseline, 183 women used DMPA and 274 were non-users. Data on depressive symptoms and on factors potentially related to DMPA use and depression were collected by questionnaires at 6-month intervals for up to 3 years.

In multivariate longitudinal analysis, an increased likelihood of reporting depressive symptoms among continuous DMPA users (OR = 1.44; 95% CI = 1.00-2.07) and discontinuers (OR = 1.60; 95% CI = 1.03-2.48) was found when compared to non-users. Women who discontinued DMPA use had elevated depressive symptoms prior to discontinuation (OR = 2.30; 95% CI = 1.42-3.70) and immediately following discontinuation (OR = 2.46; 95% CI = 1. 46-4.14), and depressive symptoms subsided at subsequent visits relative to non-users. The authors conclude that the prospective analyses found an association between DMPA use and depressive symptoms but further research was needed to determine whether the relationship is causal.

3.1.2 Gupta N, O'Brien R, Jacobsen LJ et al, 2001 (7)

This prospective study evaluated changes in negative and positive affect among adolescent females using DMPA as a contraceptive agent. Thirty-nine adolescents choosing DMPA as a contraceptive agent and 24 adolescents not using any hormonal contraception were enrolled as subjects and controls from an urban hospital adolescent clinic. Two standardized questionnaires, the Beck Depression Inventory (BDI) and the Multiple Affect Adjective Checklist-Revised (MAACL-R), were administered at baseline to all participants and readministered at 3, 6, and 12 months.

The results did not show any depressive symptoms when using DMPA as a contraceptive agent as contraception over a period of 12 months as measured by the BDI and no significant changes in negative or positive affect as measured by the MAACL-R.

***Comments*:** According to the medical library Uptodate, no consistent effects of DMPA on mood have been reported in observational studies (1). A history of depression is not a contraindication to use of DMPA. However, progestins may cause or exacerbate depressive symptoms in certain subpopulations of women, including those with a history of premenstrual syndrome or mood disorders, who therefore need therefore to be followed closely when starting progestin-based therapy.

3.2 The use of social media

A Google search shows women experiencing distressing effects after stopping Depo Provera and describing it on social media. It is hard to estimate the size of the problem. Symptoms described include breast pain, weight gain, hot flashes, nausea, headache, bloating, bone pain and sleep problems. Many of the women feel that healthcare professionals seem unable to explain their problems or to offer effective solutions.

3.2.1 Can additional information on adverse effects be found though social media?

The potential role of social media was studied as a way to complement traditional data sources to answer comparative effectiveness and safety questions on medicines in use by analysing all publically available social media data for posts mentioning inflammatory arthritis (8). Using a software platform searching all public-facing social media, content related to inflammatory arthritis and medicines used for its treatment was examined. Results showed that posts were predominantly from the US (75%) from patient authors (87%) under 40 years of age (61%). It was possible to identify medications and certain adverse effects that were more commonly discussed. Some of these effects were previously known and some were unknown.

There was a threefold increase in posts following television direct-to-consumer advertisement ($p = 0.04$) and posts expressing medication safety concerns were significantly more frequent than favourable posts. The authors conclude that social media data may be useful for hypothesis generation.

Social media may also negatively affect patient's experiences of drug treatment. A publication describes it as the nocebo effect, whereby the expectation of side effects leads to them being experienced (9). For example the news media may influence expectations, particularly when media attention is directed towards a health or medication scare.

In the case with Depo-Provera, the internet offers an explanation to the symptoms many of the women experience (10). Dr. Jerilynn C. Prior, Society for Menstrual Cycle Research board member, professor of endocrinology at the University of British Columbia, and scientific director of the Centre for Menstrual Cycle and Ovulation Research gives her thoughts to why some women feel miserable when they stop Depo-Provera:

"First let me say that I have looked in the recent medical literature and been unable to find any studies of women's experiences on stopping Depo.

Here's what I think is happening, and I've formed this understanding based on what women described in their posts: Women's reproduction has been suppressed by Depo for months or years. This means that (figuratively speaking) the hypothalamus, pituitary and ovaries have 'forgotten how' to coordinate their usual complex and amazing feedback needed for normal ovulatory menstrual cycles.

However, our bodies are programmed to work hard to regain reproduction so there is a kind of rebound over-stimulation of estrogen levels (the easiest hormone to get the ovary to produce). The result is erratic but high estrogen levels causing nausea, sore breasts, fluid retention and abdominal bloating, mood swings and heavy or prolonged vaginal bleeding.

With high estrogen levels and weight gain, plus the "hypothalamic incoordination," ovulation doesn't occur and therefore no progesterone is produced. Progesterone – the hormone produced after ovulation in normal menstrual cycles – is needed to counterbalance the high estrogen levels. I believe that it is this estrogen-progesterone imbalance that is leading to all these miserable symptoms".

3.2.2 The importance of patient information

In a randomised study, two groups (total 46 patients) of patients (overt and covert groups) received escitalopram during nine weeks for treatment of social anxiety disorder (SAD) (11). The overt group received correct information about SSRI treatment and the expected improvement, whereas the covert group were told that they would receive an active placebo, likely to induce side effects similar to escitalopram but out of which no symptom-improvement could be expected. Outcomes were

measured by fMRI scanning, the primary outcome response status LSAS-SR filled in by the patient 5 times online at home and by a public speaking behavioural test in which they had to give a two minute speech in front of an audience.

After nine weeks of treatment, overt (n=24) as compared to covert (n=22) SSRI administration yielded significantly better outcome on the LSAS-SR (adjusted difference 21.17, 95% CI 10.69–31.65, p<0.0001) with more than three times higher response rate (50% vs. 14%; $\chi 2(1)=6.91$, p=0.009) and twice the effect size (d=2.24 vs. d=1.13) from pre- to posttreatment. On fMRI outcomes, there was suggestive evidence for a differential neural response to treatment between groups. Thus, the instructions given while prescribing SSRIs make a significant clinical difference.

In another randomised study, women who received information on risks, benefits, and overall characteristics of DMPA at each visit and counselling that emphasized that potential side effects were not harmful were much less likely to discontinue the method within 12 months than the usual care group (OR 0.27, 95% CI 0.16-0.44) and much less likely to discontinue the method because of menstrual disturbances (OR 0.20, 95% CI 0.11-0.37) (12).

Comments: The lack of evidence regarding withdrawal syndrome with Depo Provera may have many explanations, the most important one being that the symptoms as well as the nature of the medicine do not necessarily fill the criteria for the reactions to be classified as a withdrawal syndrome.

Women however experience these symptoms and in addition to the discomfort, may become anxious because of concerns that the changes are due to pregnancy or gynaecologic disease. As social media is not quality controlled, proactive patient education by health professionals about what to expect and how to manage it can be an important way to reduce the concerns.

3.3 Company reports

3.3.1 Pfizer

[redacted]

[redacted]

3.4 CARM data

CARM has received 251 cases reported for Depo-Provera up until 31 December 2017. Of these, two identified withdrawal effects (see Annexe 2).

The report previously described regarded a 31 year old female who had received [redacted] Depo-Provera [redacted] November 2016. [redacted] foggy feeling in her head [redacted] virus feeling, fatigue, eye pain, visual disturbance, itching all over her body, restlessness, agitation, shaking, nausea and shortness of breath on resting. [redacted]

[redacted] Ibuprofen, Panadol, Ural, Hiprex, Domperidone, Ranitidine, Omeprazole, Magnesium, Maca and Probiotics [redacted]

The reporter [redacted] refers to forums where other women report the same symptoms on stopping Depo-Provera, for example www.steadyhealth.com/topics/do-i-have-depo-provera-withdrawal-symptoms?page=2 where people ask one MD if they have Depo-Provera withdrawal symptoms. The reporter especially refers to question number 5.

This question relates to a woman who was prescribed Depo-Provera for 5 years and discontinued because of probable bone loss. After discontinuation (the timing is not specified, but when asking the question she is about three months and a week after the last injection) she experienced diarrhea, lower abdomen pain, lower back pain, bone pain, pooping within ten minutes of eating, no appetite and tiredness. She thought she had the flu, but it was lasting too long and the symptoms would come and go.

In the second case report to CARM a 36 year old female [redacted] nausea and vomiting [redacted] Depo-Provera on [redacted] 09/2009 and [redacted] 11/2009. [redacted] nausea, bloating and menstrual irregularities a[redacted] bleeding had returned consisting of light periods, [redacted] heavy bleeding. It was unclear if these bleeding events were truly withdrawal syndrome.

3.5 International information

[redacted]

3.5.1 [redacted]

[redacted]

3.5.2 [redacted]

[redacted]

3.5.3 [redacted]

[redacted]

3.5.4 [redacted]

[redacted]

3.5.5 [redacted]

[redacted]

4.0 DISCUSSION AND CONCLUSIONS

Depo Provera (medroxyprogesterone) is a progestin indicated for contraception to be administered every third month. Two cases of withdrawal syndrome with flu like symptoms and bleeding irregularities have been reported to CARM. The term withdrawal syndrome was used by the reporter. Discontinuation syndrome may be a better description.

As a contraceptive, Depo Provera affects both progesterone and estrogen levels in the body. After discontinuation ovulation and fertility will return, but after several months.

There is not much published data available on symptoms occurring after Depo Provera discontinuation beyond research about bone density and length of time to return to fertility. On the internet women describe symptoms, often resembling known adverse effects of Depo Provera treatment. The adverse effects are included in the data sheet as well as warnings regarding disruption of menstrual bleedings, decrease of BMD and use in patients with a history of depression. Withdrawal syndrome or withdrawal symptoms are not currently included in the data sheet.

[redacted]

According to the company [redacted]

Still many women seem to have problems, which they describe on social media. Some of the symptoms may be a logical consequence of the changes to hormonal balance. These changes may affect women to a higher or a lower extent.

Women will look for answers to their unexplained experienced symptoms. It is important for healthcare professionals to provide quality controlled information about what to expect when starting and discontinuing treatment with Depo-Provera, and to follow up patients at risk.

Social media may be a way, among others, to find potential adverse effects but also a way to learn about which adverse effects (as well as effects) matter to patients.

There is not enough scientific evidence available to support including withdrawal syndrome or withdrawal symptoms in the data sheet at this time. However, the issue should continue to be monitored by Medsafe.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- You would classify the problems that these women have experienced as withdrawal symptoms?
- Any information regarding withdrawal symptoms should be included in the data sheet?
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Pfizer Depo-Provera withdrawal syndrome 2017. Response
2. CARM report

7.0 REFERENCES

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