Please read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor, nurse or healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT DEPO-PROVERA
Depo-Provera is a very effective injectable contraceptive which gives 12 weeks continuous contraception with each injection. The effect is not reversible once the injection is given.

- You must have injections of this contraceptive regularly every 12 weeks; otherwise you may risk becoming pregnant (see section 3).
- Depo-Provera may not be suitable for every woman. You will need to discuss with your doctor or healthcare professional providing your contraception on whether it is suitable for you, especially if you wish to use it for more than 2 years (See section 1).
- Depo-Provera may not be suitable for you if you have a history of certain medical conditions (see section 2) or if you are taking a medicine called aminoglutethimide that thins the blood (see section 2). Your doctor or nurse should take a full medical history before prescribing Depo-Provera.
- Regular use of Depo-Provera causes a gradual loss of bone mineral density (see section 4). For a small number of patients that were followed-up, the average bone mineral density returned to average 1-3 years after they stopped using Depo-Provera. Teenagers who are rapidly developing their bones may be at particular risk and should only use Depo-Provera if other methods of contraception have been discussed and considered unsuitable or unacceptable.
- Your doctor may plan to conduct a general medical as well as a gynaecological examination before they decide to prescribe Depo-Provera for you and may request you to visit the clinic for similar examinations at appropriate intervals thereafter.

What is in this leaflet
1. What Depo-Provera is and what it is used for
2. What you need to know before you use Depo-Provera
3. How to use Depo-Provera
4. Possible side effects
5. How to store Depo-Provera
6. Contents of the pack and other information

1. What Depo-Provera is and what it is used for

Depo-Provera is a long acting contraceptive. This medicine contains medroxyprogesterone acetate (MPA), which is one of a group of medicines called ‘Progestogens’. It is similar to (but not the same as) the natural hormone, progesterone that is produced in the ovaries during the second half of your menstrual cycle.
Depo-Provera acts by preventing an egg from fully developing and being released from the ovaries during your menstrual cycle. If an egg is not released it cannot become fertilised by sperm and result in pregnancy. Depo-Provera also causes changes in the lining of your womb that makes it less likely for pregnancy to occur. It also thickens the mucus at the entrance of the womb, making it more difficult for sperm to enter.

Depo-Provera can be used:
- For long-term contraception where you and the person who provides your contraception (e.g. your doctor or healthcare professional) have decided that this method is the most suitable for you.
- If you wish to use Depo-Provera for more than 2 years your doctor or healthcare professional may wish to re-evaluate the risks and benefits of using Depo-Provera to make sure that it is still the best option for you.
- In teenagers only after other methods of contraception have been discussed with the healthcare professional who provides your contraception and considered to be unsuitable or unacceptable.
- For just one or two occasions in the following cases:
  - if your partner is undergoing a vasectomy, to give you protection until the vasectomy becomes effective
  - if you are being immunised against rubella, to prevent pregnancy during the period of activity of the virus
  - if you are awaiting sterilisation.

2. What you need to know before you use Depo-Provera

**Do not use Depo-Provera:**
- If you are allergic (hypersensitive) to the active ingredient (MPA) or any of the other ingredients (listed in section 6). There is a small risk of a severe allergic reaction to Depo-Provera that will require emergency medical treatment.
- If you think you may be pregnant.
- If you have had, or think you may have, hormone-dependent cancer of the breast or reproductive organs.
- If you have unexplained bleeding from the womb (uterus).
- If you have liver disease.
- If you have not yet started your periods.

**Warnings and precautions**
Talk to your doctor or healthcare professional before using Depo-Provera.

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

- Migraine headaches – if you develop migraine you should consult your doctor before receiving further injections of Depo-Provera
- Diabetes or a family history of diabetes
- Severe pain or swelling in the calf (indicating a possible clot in the leg, which may be called phlebitis)
- Blood clotting disorders such as deep vein thrombosis (blood clot in the legs), pulmonary embolus (blood clot in the lung) or a stroke you should not receive further injections of Depo-Provera
- Problems with your eyesight while using Depo-Provera; for example a sudden partial or complete loss of vision or double vision
• Past history of or current depression
• Problems with your liver or liver disease
• Problems with your kidneys or kidney disease
• History of heart disease or cholesterol problems including any family history
• If you have recently had a ‘hydatidiform mole’ which is a type of abnormal pregnancy
• Asthma
• Epilepsy
• If you are using certain medicines such as high dose glucocorticoids (steroids), anti-epileptics, and thyroid hormones. Tell the person who provides your contraception if you are taking these or any other medicines - they may recommend a more suitable method of contraception.

Cervical smear testing:
The results of a cervical smear and some laboratory tests could also be affected if you are using Depo-Provera so it is important that you tell your doctor.

Protection against sexually transmitted diseases:
Depo-Provera does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Other medicines and Depo-Provera:
• Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
• Tell your doctor or healthcare professional if you are taking a medicine called aminoglutethiamide or other medicines that thin your blood (anticoagulants) as these may affect the way Depo-Provera works.
• Always tell your doctor or healthcare professional who treats you that you are using Depo-Provera as a contraceptive if you are taking or have recently taken any other medicines, even those you bought yourself without a prescription, because medicines can sometimes interact with each other.

Pregnancy:
• Your doctor will check that you are not pregnant before giving you the first injection and also if any following injection is delayed beyond 89 days (12 weeks and 5 days).
• Depo-Provera must not be taken if you are pregnant as hormonal medicines can affect the developing baby.
• If you think you may have become pregnant while using Depo-Provera for contraception, tell your doctor immediately.

Effect on future fertility:
• Your usual level of fertility should return when the effect of the injection has worn off.
• This takes different amounts of time in different women, and does not depend on how long you have been using Depo-Provera.
• In studies, over 80% of women trying to get pregnant conceived within 15 months of the last injection; however this varied from 4 months after the last injection to more than two years.
• Some women have got pregnant as early as 14 weeks after their last injection.

If you are breast-feeding:
- Depo-Provera does not prevent the breast from producing milk so nursing mothers can use it; however, it is better for the baby that for the first few weeks after birth its mother’s milk contains no traces of any medicines, including Depo-Provera.
- Your doctor or healthcare professional may advise that you wait until at least 6 weeks after your baby has been born before you start using Depo-Provera for contraception.
- If a baby is exposed to Depo-Provera in the breast milk, no harmful effects have been seen in babies and children.

**Driving and using machines:**
Depo-Provera may cause headaches and dizziness. Therefore be careful until you know whether this medicine affects your ability to drive or use machines. If you have any concerns discuss them with your doctor.

**Depo-Provera contains methylparaben (E218), propylparaben (E216) and sodium:**
Methylparaben and propylparaben may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
This medicinal product contains less than 1 mmol sodium (23 mg) per 150 mg/ml, i.e. essentially ‘sodium free’.

3. How to use Depo-Provera

**This medicine will be given to you by your doctor or healthcare professional.**
(The last section of this leaflet contains instructions for your doctor or healthcare professional on how they should do this.)

Depo-Provera is given every 12 weeks as a single intramuscular injection of 1 ml (150 mg medroxyprogesterone acetate) into the buttock or upper arm. The injection is given during the first 5 days after the beginning of a normal menstrual period.

Following childbirth the first Depo-Provera injection can be given within 5 days after childbirth if you are not breast-feeding.

Provided that the injection is given at the times stated above, then you are protected from pregnancy straight away and there is no need to take extra precautions.

Depo-Provera works as a contraceptive for 12 weeks in your body. There is no way of reversing the injection once it is given.

For effective contraceptive cover, Depo-Provera MUST be given every 12 weeks. Make sure that you or your doctor makes your next appointment for 12 weeks time.

The risk of heavy or pro-longed vaginal bleeding may be increased if Depo-Provera is used immediately following childbirth or termination of pregnancy.

**If you forget an injection of Depo-Provera:**
If you forget your injection or are late getting your next injection (i.e. wait longer than 12 weeks between injections), there is a greater risk that you could become pregnant. Ask your doctor or healthcare professional to find out when you should receive your next injection of Depo-Provera and which type of contraception should be used in the meantime.

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

If you have any further questions on the use of this medicine, ask your doctor or healthcare professional.

4. Possible side effects
Like all medicines, this medicine can cause side effects although not everybody gets them.

There is a low risk of anaphylactic responses (serious allergic reactions which may need urgent medical attention or hospitalization). Possible symptoms include: swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing, skin rashes, shock or collapse.

Deep vein thrombosis (DVT) is a condition in which a blood clot forms in one of your deep veins, usually in your leg. Signs of possible DVT include: swelling of the affected leg, pain and tenderness in the affected leg (you may also find it difficult to stand properly with your full weight on the affected leg), a change in the colour of your skin, for example, redness or skin that feels warm or hot to the touch.

Women who use Depo-Provera tend to have lower bone mineral density than women of the same age who have never used it. The effects of Depo-Provera are greatest in the first 2-3 years of use. Following this, bone mineral density tends to stabilise and there appears to be some recovery when Depo-Provera is stopped. It is not yet possible to say whether Depo-Provera increases the risk of osteoporosis (weak bones) and fractures in later life.

Tell your doctor immediately if you experience any of the above symptoms.

The following other side effects may occur:

**Common** (may affect up to 1 in 10 people)
Abdominal pain or discomfort, bloating, feeling sick, vaginal discharge or inflammation, changes in appetite, back pain, headaches, dizziness, irregular periods, very light or no periods (amenorrhoea), breast pain or tenderness, pelvic pain, hot flushes, acne, hair loss, rash, weakness or tiredness, injection site reactions, feeling of weakness, tingling or numbness in the hands and feet, depression, nervousness, insomnia (difficulty sleeping), irritability, anorgasmia (failure to climax during sexual intercourse), emotional disturbance, intermenstrual bleeding (bleeding between periods), menorrhagia (heavy periods).

**Uncommon** (may affect up to 1 in 100 people)
Jaundice (this will cause yellowing of the skin and the whites of the eyes), hypertension, varicose veins, thrombophlebitis (inflammation of part of a vein), pulmonary embolism (blood clot in the lungs which causes chest pain and breathlessness), allergic reactions (such as swelling on the face and throat), abnormal liver enzymes (blood tests used to measure liver function), feeling of dizziness or ‘spinning’, abdominal discomfort, change in weight, fluid retention, joint pain, muscle cramps, pain in legs and arms, somnolence (sleepiness), migraine, convulsion (‘fit’), vaginal dryness, painful periods, change in breast size, painful intercourse, ovarian cyst, premenstrual syndrome, infections of the urinary tract or reproductive organs, an increase in thickness of the lining of the womb, dark patches on the skin, bruising, excessive hair growth, itching, skin rash, swelling, chest pain, fever, abnormal cervical smear results, anxiety, difficulty breathing.

**Rare** (may affect up to 1 in 1,000 people)
Tachycardia (faster heart beat), breast lumps or nipple bleeding, thirst, hoarseness, rectal bleeding (bleeding from the anus), paralysis, decreased glucose tolerance (abnormal blood sugar levels), breast cancer, anaemia (reduction in red blood cells which can make the skin
pale and cause weakness or breathlessness).

**Not known** (frequency cannot be estimated from the available data):
Blood clotting disorders, deep vein thrombosis (blood clots forming in the veins, usually the legs), disturbed liver function. Osteoporosis (thinning of the bones) including fractures, loss of bone mineral density (a test to measure the strength of bones), swelling of ankles or wrists, abnormal uterine bleeding (irregular, increase, decrease), milky discharge from breasts in women who are not breastfeeding, vaginal cysts, milk supply stopping (in breastfeeding mothers), feeling pregnant, delay in becoming pregnant after stopping Depo-Provera, scaling of skin, scleroderma (a rare autoimmune disease that affects the skin and other parts of the body), weakness in the face muscles, fainting, blood disorder, skin striae (stretch marks).

**Possible effect on your periods:**
Depo-Provera will usually disturb the pattern of a woman’s period. After the first injection it is most likely that you will have irregular, possibly lengthy bleeding or spotting. This will continue in some women. This is quite normal and nothing to worry about.

One third of women will not have any bleeding at all after the first injection. After 4 injections, most women find that their periods have stopped completely. Not having periods is nothing to worry about.

If you experience very heavy or prolonged bleeding you should talk to your doctor. This happens rarely but can be treated.

When you stop taking Depo-Provera your periods will return to normal in a few months.

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

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

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g. epilepsy medication or steroids
- Low body mass index or eating disorder, e.g. anorexia nervosa or bulimia
- Previous low trauma fracture that was not caused by a fall
- Strong family history of osteoporosis
Teenagers (up to 18 years): Normally, the bones of teenagers are rapidly growing and increasing in strength. The stronger the bones are when adulthood is reached, the greater the protection against osteoporosis in later life. Since Depo-Provera may cause teenage bones to become thinner at a time when they should be growing, its effect may be particularly important in this age group. Bones start to recover when Depo-Provera is stopped, but it is not yet known whether the bone mineral density reaches the same levels as it would have if Depo-Provera had never been used. **You should therefore discuss whether another form of contraception might be more suitable for you with the person who provides your contraception before starting Depo-Provera.**

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

**Possible risk of cancer:**
Studies of women who have used different forms of contraception found that women who used Depo-Provera for contraception had no increase in overall risk of developing cancer of the ovary, womb, cervix or liver.

**Possible risk of breast cancer**
Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives. Depo-Provera may increase the risk of breast cancer slightly compared with women who have never used it. However, any excess risk is small in relation to the overall risk of breast cancer, particularly in young women.

Older women have a higher baseline risk of breast cancer and therefore the increase in the number of cases due to Depo-Provera is greater in older women than in younger women.

In absolute terms this means that:

A 15 year old who uses Depo-Provera for **5 years** increases her chance of developing breast cancer by a negligible amount by the age of 30.

A 25 year old who uses Depo-Provera for **5 years** increases her chance of developing breast cancer by the age of 40 from **44 cases** per 10,000 women (without Depo-Provera use) to up to **47 cases** per 10,000 women i.e. an extra 3 cases/10,000.

A 35 year old who uses Depo-Provera for **5 years** increases her chance of developing breast cancer by the age of 50 from **160 cases** per 10,000 women (without Depo-Provera use) to **170 cases** per 10,000 women i.e. an extra 10 cases/10,000.

**Possible risk of forming an abscess at the injection site:**
As with any intramuscular injection, there is a risk of an abscess forming at the site of injection. This may require medical or surgical attention.

**Possible risk of weight gain:**
Some women gained weight while using Depo-Provera. Studies show that over the first 1-2 years of use, the average weight gain was 5-8 lbs. Women completing 4-6 years of therapy gained an average of 14-16.5 lbs.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). By reporting side effects you can help provide more information on the safety of this medicine.
5. How to store Depo-Provera

Keep out of the sight and reach of children.
Do not store above 25°C and protect from freezing.
Do not use Depo-Provera after the last day of the month shown in the expiry date stated on the pre-filled syringe label and the carton after EXP. The expiry date is the last day of that month.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Depo-Provera contains:
The active ingredient in Depo-Provera is medroxyprogesterone acetate (MPA). Each dose (1 millilitre) of Depo-Provera contains 150 mg of medroxyprogesterone acetate. Depo-Provera also contains methylparaben (E218), Macrogol 3350, polysorbate 80, propylparaben (E216), sodium chloride and water. Hydrochloric acid or sodium hydroxide may also be added when the product is being made to adjust the acidity or alkalinity of the product to the correct level.

What Depo-Provera looks like and contents of the pack:
Depo-Provera is a white sterile suspension. Each syringe contains 1 millilitre (ml) of Depo-Provera. Depo-Provera is supplied in cartons containing one prefilled syringe.

Marketing Authorisation Holder
Pfizer Limited
Ramsgate Road
Sandwich
CT13 9NJ
United Kingdom

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

Company Contact Address
For any further information about this medicinal product, please contact Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. Telephone 01304 616161

This leaflet was last revised in 10/2013.

Ref.: DP 6_4
The following information is intended for medical or healthcare professionals only:
(For further information, consult the Summary of Product Characteristics.)

Description
Depo-Provera is a white, sterile suspension for injection. Each 1 ml contains 150 mg medroxyprogesterone acetate. Excipients are methylparaben (E218), macrogol 3350, polysorbate 80, propylparaben (E216), sodium chloride, water for injection. Hydrochloric acid or sodium hydroxide may be present as pH adjusters.

Uses
Depo-Provera is a long-term contraceptive agent suitable for use in women who have been appropriately counselled concerning the likelihood of menstrual disturbance and the potential for a delay in return to full fertility.
Depo-Provera may also be used for short-term contraception in the following circumstances:
(i) For partners of men undergoing vasectomy, for protection until the vasectomy becomes effective.
(ii) In women who are being immunised against rubella, to prevent pregnancy during the period of activity of the virus.
(iii) In women awaiting sterilisation.

Since loss of bone mineral density (BMD) may occur in females of all ages who use Depo-Provera injection long-term, a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Use in adolescents (12 – 18 years)
In adolescents, Depo-Provera may be used, but only after other methods of contraception have been discussed with the patient and considered unsuitable or unacceptable.

It is of the greatest importance that adequate explanations of the long-term nature of the product, of its possible side-effects and of the impossibility of immediately reversing the effects of each injection are given to potential users and that every effort is made to ensure that each patient receives such counselling as to enable her to fully understand these explanations. Patient information leaflets are supplied by the manufacturer. It is recommended that the doctor uses these leaflets to aid counselling of the patient before giving the injection of Depo-Provera.

Consistent with good clinical practice, a general medical as well as a gynaecological examination should be undertaken before administration of Depo-Provera and at appropriate intervals thereafter.

Dosage
Each ml of suspension contains 150 mg medroxyprogesterone acetate. The sterile aqueous suspension of Depo-Provera should be vigorously shaken just before use to ensure that the dose being given represents a uniform suspension of Depo-Provera. Doses should be given by deep intramuscular injection into the buttock or arm.
Care should be taken to ensure that the depot injection is given into the muscle tissue, preferably the gluteus maximus, but other muscle tissue such as the deltoid may be used and the site of injection should be cleansed using standard methods prior to administration of the injection.
Assembly of syringe for single use:
1. Remove tip cap.
2. Position needle using aseptic technique.
3. Remove needle shield. The syringe is now ready for use.

Administration

Adults

First injection: To provide contraceptive cover in the first cycle of use, an injection of 150 mg i.m. should be given during the first five days of a normal menstrual cycle. If the injection is carried out according to these instructions, no additional contraceptive cover is required.

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

There is evidence that women prescribed Depo-Provera in the immediate puerperium can experience prolonged and heavy bleeding. Because of this, the drug should be used with caution in the puerperium. Women who are considering use of the product immediately following delivery or termination should be advised that the risk of heavy or prolonged bleeding may be increased.

Doctors are reminded that in the non breast-feeding postpartum patient, ovulation may occur as early as week 4. If the puerperal woman will be breast-feeding, the initial injection should be given no sooner than six weeks postpartum, when the infant’s enzyme system is more fully developed. Further injections should be given at 12 week intervals.

Further doses: These should be given at 12 week intervals, however, as long as the injection is given no later than five days after this time, no additional contraceptive measures (e.g. barrier) are required.

(NB For partners of men undergoing vasectomy a second injection of 150 mg i.m. 12 weeks after the first may be necessary in a small proportion of patients where the partner’s sperm count has not fallen to zero.) If the interval from the preceding injection is greater than 89 days (12 weeks and five days) for any reason, then pregnancy should be excluded before the next injection is given and the patient should use additional contraceptive measures (e.g. barrier) for fourteen days after this subsequent injection.

Paediatric population (12-18 years): Depo-Provera is not indicated before menarche. Data in adolescent females (12-18 years) is available. Other than concerns about loss of BMD, the safety and effectiveness of Depo-Provera is expected to be the same for adolescents after menarche and adult females.

Switching from other Methods of Contraception: Depo-Provera should be given in a manner that ensures continuous contraceptive coverage. This should be based upon the mechanism of action of other methods (e.g. patients switching from oral contraceptives should have their first injection of Depo-Provera within 7 days of taking their last active pill).

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

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

Contraindications

Depo-Provera is contraindicated in patients with a known sensitivity to medroxyprogesterone acetate or any ingredient of this medicine.

Depo-Provera should not be used during pregnancy, either for diagnosis or therapy.

Depo-Provera is contraindicated as a contraceptive at the above dosage in known or suspected hormone-dependent malignancy of breast or genital organs.
Depo-Provera is contraindicated in patients with the presence or history of severe hepatic disease whose liver function tests have not returned to normal. Whether administered alone or in combination with oestrogen, Depo-Provera should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital tract malignancy eliminated.

**Special warnings and precautions for use**

**Warnings:**

*Loss of Bone Mineral Density:*

Use of Depo-Provera 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; however BMD appears to increase after Depo-Provera 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 Depo-Provera by younger women will reduce peak bone mass and increase the risk for fracture in later life.

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

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

Significant risk factors for osteoporosis include:

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

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

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

*Menstrual Irregularity:* The administration of Depo-Provera usually causes disruption of the normal menstrual cycle. Bleeding patterns include amenorrhoea (present in up to 30% of women during the first 3 months and increasing to 55% by month 12 and 68% by month 24); irregular bleeding and spotting; prolonged (>10 days) episodes of bleeding (up to 33% of women in the first 3 months of use decreasing to 12% by month 12). Rarely, heavy prolonged
bleeding may occur. Evidence suggests that prolonged or heavy bleeding requiring treatment may occur in 0.5-4 occasions per 100 women years of use. If abnormal bleeding persists or is severe, appropriate investigation should take place to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary. Excessive or prolonged bleeding can be controlled by the co-administration of oestrogen. This may be delivered either in the form of a low dose (30 micrograms oestrogen) combined oral contraceptive pill or in the form of oestrogen replacement therapy such as conjugated equine oestrogen (0.625-1.25 mg daily). Oestrogen therapy may need to be repeated for 1-2 cycles. Long-term co-administration of oestrogen is not recommended.

Return to Fertility: There is no evidence that Depo-Provera causes permanent infertility. Pregnancies have occurred as early as 14 weeks after a preceding injection, however, in clinical trials, the mean time to return of ovulation was 5.3 months following the preceding injection. Women should be counselled that there is a potential for delay in return to full fertility following use of the method, regardless of the duration of use, however, 83% of women may be expected to conceive within 12 months of the first "missed" injection (i.e. 15 months after the last injection administered). The median time to conception was 10 months (range 4-31) after the last injection.

Cancer Risks: Long-term case-controlled surveillance of Depo-Provera users found no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users. Breast cancer is rare among women under 40 years of age whether or not they use hormonal contraceptives.

Results from some epidemiological studies suggest a small difference in risk of the disease in current and recent users compared with never-users. Any excess risk in current and recent DMPA users is small in relation to the overall risk of breast cancer, particularly in young women (see below), and is not apparent after 10 years since last use. Duration of use does not seem to be important.

Possible number of additional cases of breast cancer diagnosed up to 10 years after stopping injectable progestogens*

<table>
<thead>
<tr>
<th>Age at last use of DMPA</th>
<th>No of cases per 10,000 women who are never-users</th>
<th>Possible additional cases per 10,000 DMPA users</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Less than 1</td>
<td>Much less than 1</td>
</tr>
<tr>
<td>30</td>
<td>44</td>
<td>2-3</td>
</tr>
<tr>
<td>40</td>
<td>160</td>
<td>10</td>
</tr>
</tbody>
</table>

*based on use for 5 years

Weight Gain: There is a tendency for women to gain weight while on Depo-Provera therapy. Studies indicate that over the first 1-2 years of use, average weight gain was 5-8 lbs. Women completing 4-6 years of therapy gained an average of 14-16.5 lbs. There is evidence that weight is gained as a result of increased fat and is not secondary to an anabolic effect or fluid retention.

Anaphylaxis: Reports of anaphylactic responses (anaphylactic reactions, anaphylactic shock, anaphylactoid reactions) have been received.

Thromboembolic Disorders: Should the patient experience pulmonary embolism, cerebrovascular disease or retinal thrombosis while receiving Depo-Provera, the drug should not be readministered.
Psychiatric Disorders: Patients with a history of endogenous depression should be carefully monitored. Some patients may complain of premenstrual-type depression while on Depo-Provera therapy.

Abscess formation: As with any intramuscular injection, especially if not administered correctly, there is a risk of abscess formation at the site of injection, which may require medical and/or surgical intervention.

Precautions:
History or emergence of the following conditions requires careful consideration and appropriate investigation: migraine or unusually severe headaches, acute visual disturbances of any kind, pathological changes in liver function and hormone levels. Patients with thromboembolic or coronary vascular disease should be carefully evaluated before using Depo-Provera.
A decrease in glucose tolerance has been observed in some patients treated with progestogens. The mechanism for this decrease is obscure. For this reason, diabetic patients should be carefully monitored while receiving progestogen therapy.
Rare cases of thromboembolism have been reported with use of Depo-Provera, but causality has not been established.
The effects of medroxyprogesterone acetate on lipid metabolism have been studied with no clear impact demonstrated. Both increases and decreases in total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol have been observed in studies. The use of Depo-Provera appears to be associated with a 15-20% reduction in serum high density lipoprotein (HDL) cholesterol levels which may protect women from cardiovascular disease. The clinical consequences of this observation are unknown.
The potential for an increased risk of coronary disease should be considered prior to use. Doctors should carefully consider the use of Depo-Provera in patients with recent trophoblastic disease before levels of human chorionic gonadotrophin have returned to normal.
Physicians should be aware that pathologists should be informed of the patient’s use of Depo-Provera if endometrial or endocervical tissue is submitted for examination.
The results of certain laboratory tests may be affected by the use of Depo-Provera. These include gonadotrophin levels (decreased), plasma progesterone levels (decreased), urinary pregnanediol levels (decreased), plasma oestrogen levels (decreased), plasma cortisol levels (decreased), glucose tolerance test, metyrapone test, liver function tests (may increase), thyroid function tests (protein bound iodine levels may increase and T3 uptake levels may decrease). Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX and X may increase.

Interaction with other medicinal products and other forms of interaction
Aminoglutethimide administered concurrently with Depo-Provera may significantly depress the bioavailability of Depo-Provera.
Interactions with other medicinal treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interaction 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 the kinetics of medroxyprogesterone acetate. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.
Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.
**Fertility, pregnancy and lactation**

Doctors should check that patients are not pregnant before the initial injection of Depo-Provera, and also if administration of any subsequent injection is delayed beyond 89 days (12 weeks and five days).

Infants from accidental pregnancies that occur 1-2 months after injection of Depo-Provera may be at an increased risk of low birth weight, which in turn is associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon. Children exposed to medroxyprogesterone acetate in utero and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Medroxyprogesterone acetate and/or its metabolites are secreted in breast milk, but there is no evidence to suggest that this presents any hazard to the child. Infants exposed to medroxyprogesterone acetate via breast milk have been studied for developmental and behavioural effects to puberty. No adverse effects have been noted.

**Effects on ability to drive and use machines**

Depo-Provera may cause headaches and dizziness. Patients should be advised not to drive or operate machinery if affected.

**Undesirable effects**

In a large clinical trial of over 3900 women, who were treated with Depo-Provera for up to 7 years, the following adverse events were reported.

The following adverse events were commonly (by more than 5% of subjects) reported: menstrual irregularities (bleeding and/or amenorrhoea), weight changes, headache, nervousness, abdominal pain or discomfort, dizziness, asthenia (weakness or fatigue). Adverse events reported by 1% to 5% of subjects using Depo-Provera were: decreased libido or anorgasmia, backache, leg cramps, depression, nausea, insomnia, leucorrhoea, acne, vaginitis, pelvic pain, breast pain, no hair growth or alopecia, bloating, rash, oedema, hot flushes.

Adverse reactions are listed according to the following categories:

**Very Common >10%, Common ≥1% and < 10%, Uncommon >0.1% and <1%, Rare < 0.1%, Not known (frequency cannot be estimated from the available data)**

- **Ear and Labyrinth Disorders:** Uncommon: Vertigo.
- **Infection & Infestations:** Common: Vaginitis.
- **Metabolism & Nutrition Disorders:** Common: Appetite decrease, appetite increase. Uncommon: Weight increase, weight decrease, fluid retention.
- **Reproductive System & Breast Disorders:** Common: Amenorrhrea, breast pain/tenderness, intermenstrual bleeding, menometrorrhagia, menorrhagia, pelvic pain, leucorrhoea. Uncommon: Vaginal discharge, vulvovaginal dryness, dysmenorrhoea, change in breast size, dyspareunia, ovarian cyst, premenstrual syndrome, genitourinary infection, uterine hyperplasia. Rare: Breast lumps or nipple bleeding. Not known: Abnormal uterine bleeding (irregular, increase, decrease), galactorrhoea, vaginal cysts, prevention of lactation, sensation of pregnancy, lack of return to fertility.
Cardiovascular Disorders: Rare: Tachycardia.
Immune System Disorders: Uncommon: Hypersensitivity reactions (e.g. anaphylaxis & anaphylactoid reactions, angioedema).
General Disorders and Administration Site Conditions: Common: Fatigue, injection site reactions (such as pain or abscess), asthenia, paraesthesia. Uncommon: Chest pain, pyrexia. Rare: Thirst, hoarseness, paralysis. Not known: Facial palsy.
Investigations: Uncommon: Cervical smear abnormal. Rare: Decreased glucose tolerance.
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Rare: Breast cancer.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

**Overdose**
No positive action is required other than cessation of therapy.

**Pharmacodynamic properties**
Pharmacotherapeutic group: Progestogens, ATC code: G03AC06
Medroxyprogesterone acetate exerts anti-oestrogenic, anti-androgenic and antigonadotrophic effects.

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

<table>
<thead>
<tr>
<th>Time on Treatment</th>
<th>Lumbar Spine</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>N: 166</td>
<td>Mean % Change (95% CI): -2.7 (-3.1 to -2.3)</td>
<td>N: 166</td>
</tr>
<tr>
<td>2 year</td>
<td>N: 106</td>
<td>Mean % Change (95% CI): -4.1 (-4.6 to -3.5)</td>
<td>N: 106</td>
</tr>
</tbody>
</table>

In another controlled, clinical study adult women using medroxyprogesterone acetate injection (150 mg IM) for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years.
Mean changes in lumbar spine BMD of −2.86%, -4.11%, -4.89%, -4.93% and −5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 2 below for further details. After stopping use of medroxyprogesterone acetate injection (150 mg IM), BMD increased towards baseline values during the post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery.

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

<table>
<thead>
<tr>
<th>Time in Study</th>
<th>Spine</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td>Control</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td>5 years*</td>
<td>-5.38%</td>
<td>n=33</td>
<td>n=105</td>
</tr>
<tr>
<td>7 years**</td>
<td>-3.13%</td>
<td>n=12</td>
<td>n=60</td>
</tr>
</tbody>
</table>

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

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

BMD Changes in Adolescent Females (12-18 years)
Results from an open-label, non-randomised, clinical study of medroxyprogesterone acetate Injection (150 mg IM every 12 weeks for up to 240 weeks (4.6 years), followed by post-treatment measurements) in adolescent females (12-18 years) also showed that medroxyprogesterone acetate IM use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks (4.6 years); mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. Post-treatment follow-up showed that, based on mean values, lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued and that hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued. However, it is important to note that a large number of subjects discontinued from the study, therefore these results are based on a small number of subjects (n=71 at 60 weeks and n=25 at 240 weeks after treatment discontinuation). In contrast, a non-comparable cohort of unmatched, untreated subjects, with different baseline bone parameters from the DMPA users, showed mean BMD increases at 240 weeks of 6.4%, 1.7% and 1.9% for lumbar spine, total hip and femoral neck, respectively.

Pharmacokinetic properties
Parenteral medroxyprogesterone acetate (MPA) is a long acting progestational steroid. The long duration of action results from its slow absorption from the injection site. Immediately after injection of 150 mg/ml MPA, plasma levels were 1.7 ± 0.3 nmol/l. Two weeks later, levels were 6.8 ± 0.8 nmol/l. Concentrations fell to the initial levels by the end of 12 weeks. At lower doses, plasma levels of MPA appear directly related to the dose administered. Serum accumulation over time was not demonstrated. MPA is eliminated via faecal and urinary excretion. Plasma half-life is about six weeks after a single intramuscular injection. At least 11 metabolites have been reported. All are excreted in the urine, some, but not all, conjugated.
Shelf life
3 years
The expiry date is printed on the pre-filled syringe label and carton after EXP. The date refers to the last day of that month. Do not use Depo-Provera after this date.

Storage of the product
Do not store above 25°C and protect from freezing. Do not mix with other agents. Discard any remaining contents after use.

Name and address of the manufacturer
Pfizer Manufacturing Belgium NV/SA, Rijksweg 12, B-2870 Puurs, Belgium.

Name and address of the PL holder
Pfizer Limited, Ramsgate Road, Sandwich, CT13 9NJ, UK.

This leaflet was last revised in 10/2013

Depo-Provera is a registered trademark

Ref.: DP 5_3