

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020246Orig1s025

***Trade Name:* DEPO-PROVERA**

***Generic Name:* medroxyprogesterone acetate injectable suspension**

***Sponsor:* Pfizer, Inc.**

***Approval Date:* 11/17/2004**

***Indications:* DEPO-PROVERA CI is indicated only for the prevention of pregnancy.**

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 20-246/S-025

Pfizer, Inc.
Attention: Alan Traettino
Regulatory Affairs
235 East 42nd Street 150/7/16
New York, NY 10017

Dear Mr. Traettino:

Please refer to your supplemental new drug application (NDA) submitted September 8, 2004, received September 9, 2004, under section 505(b) of the Federal Food, Drugs, and Cosmetics Act for DEPO-PROVERA[®] Contraceptive Injection (medroxyprogesterone acetate injectable suspension) IM.

We also acknowledge receipt of your submissions dated September 28 and 30, October 13 and 25, and November 4, 2004.

This "Changes Being Effected" supplemental new drug application provides for changes to the physician and patient insert of the label.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 4, 2004 and as enclosed.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-246/S-025." Approval of this submission by FDA is not required before the labeling is used.

We request that you submit a copy of the "Dear Health Care Professional" letter communicating important information about this drug product to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 20-246/S-025

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If you have any questions, call Charlene Williamson, Regulatory Project Management Staff, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Donna Griebel
11/17/04 02:26:54 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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LABELING

Physician Information

Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.

It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate. (See WARNINGS.)

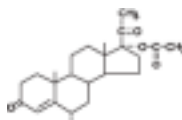
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

DEPO-PROVERA Contraceptive Injection (CI) contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white; odorless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6 α -).

The structural formula is as follows:



medroxyprogesterone acetate

DEPO-PROVERA CI for intramuscular (IM) injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

Each mL contains:

| | |
|-----------------------------|----------|
| Medroxyprogesterone acetate | 150 mg |
| Polyethylene glycol 3350 | 28.9 mg |
| Polysorbate 80 | 2.41 mg |
| Sodium chloride | 8.68 mg |
| Methylparaben | 1.37 mg |
| Propylparaben | 0.150 mg |
| Water for injection | qs |

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or

both.

CLINICAL PHARMACOLOGY

DEPO-PROVERA CI (medroxyprogesterone acetate), when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions produce its contraceptive effect.

Following a single 150 mg IM dose of DEPO-PROVERA Contraceptive Injection, medroxyprogesterone acetate concentrations, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 to 200 days following injection. Using an unextracted radioimmunoassay procedure for the assay of medroxyprogesterone acetate in serum, the apparent half-life for medroxyprogesterone acetate following IM administration of DEPO-PROVERA Contraceptive Injection is approximately 50 days.

Women with lower body weights conceive sooner than women with higher body weights after discontinuing DEPO-PROVERA Contraceptive Injection.

The effect of hepatic and/or renal disease on the pharmacokinetics of DEPO-PROVERA Contraceptive Injection is unknown.

INDICATIONS AND USAGE

DEPO-PROVERA CI is indicated only for the prevention of pregnancy. The loss of bone mineral density (BMD) in women of all ages and the impact on peak bone mass in adolescents should be considered, along with the decrease in BMD that occurs during pregnancy and/or lactation, in the risk/benefit assessment for women who use Depo-Provera CI long-term (see WARNINGS.) It is a long-term injectable contraceptive in women when administered at 3-month (13-week) intervals. Dosage does not need to be adjusted for body weight.

In five clinical studies using DEPO-PROVERA CI, the 12-month failure rate for the group of women treated with DEPO-PROVERA CI was zero (no pregnancies reported) to 0.7 by Life-Table method. Pregnancy rates with contraceptive measures are typically reported for only the first year of use as shown in Table 1. Except for intrauterine devices (IUD), implants, sterilization, and DEPO-PROVERA CI, the efficacy of these contraceptive measures depends in part on the reliability of use. The effectiveness of DEPO-PROVERA CI is dependent on the patient returning every 3 months (13 weeks) for reinjection.

Table 1
Lowest Expected and Typical Failure Rates*
Expressed as Percent of Women Experiencing
an Accidental Pregnancy
in the First Year of Continuous Use

| Method | Lowest Expected | Typical |
|--|--------------------|---------|
| Injectable progestogen DEPO-PROVERA | 0.3 | 0.3 |
| Implants Norplant (6 capsules) | 0.2† | 0.2† |
| Female sterilization | 0.2 | 0.4 |
| Male sterilization | 0.1 | 0.15 |
| Pill | | 3 |
| Combined | 0.1 | |
| Progestogen only | 0.5 | |

| Method | Lowest Expected | Typical |
|---------------------|--------------------|---------|
| IUD | | 3 |
| Progestasert | 2 | |
| Copper T 380A | 0.8 | |
| Condom | 2 | 12 |
| Diaphragm | 6 | 18 |
| Cap | 6 | 18 |
| Spermicides | 3 | 21 |
| Sponge | | |
| Parous women | 9 | 28 |
| Nulliparous women | 6 | 18 |
| Periodic abstinence | 1-9 | 20 |
| Withdrawal | 4 | 18 |
| No method | 85 | 85 |

Source: Trussell et al¹

* Lowest expected - when used exactly as directed.

Typical - includes those not following directions exactly.

† from Norplant[®] package insert.

CONTRAINDICATIONS

1. Known or suspected pregnancy or as a diagnostic test for pregnancy.
2. Undiagnosed vaginal bleeding.
3. Known or suspected malignancy of breast.
4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
5. Significant liver disease.
6. Known hypersensitivity to DEPO-PROVERA CI (medroxyprogesterone acetate or any of its other ingredients).

WARNINGS

1. Loss of Bone Mineral Density

Use of Depo-Provera CI reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD) as bone metabolism accommodates to a lower estrogen level. 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 CI by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adults and adolescents, the decrease in BMD appears to be at least partially reversible after Depo-Provera CI is discontinued and ovarian estrogen production increases. A study to assess the reversibility of loss of BMD in adolescents is ongoing.

Depo-Provera CI should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate. BMD should be evaluated when a woman needs to continue to use Depo-Provera CI long term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of Depo-Provera CI in women with osteoporosis risk factors. Depo-Provera CI can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids). Although there are no studies addressing whether calcium and Vitamin D may lessen BMD loss in women using Depo-Provera CI, all patients should have adequate calcium and Vitamin D intake.

BMD Changes in Adult Women

In a controlled, clinical study, adult women using Depo-Provera CI for up to 5 years showed spine and hip BMD mean decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4, and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of Depo-Provera CI (150 mg), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. Table 2 shows the extent of recovery of BMD for women who completed 5 years of treatment.

Table 2. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort

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

*The treatment group consisted of women who received Depo-Provera Contraceptive Injection for 5 years and were then followed for 2 years post-use.

**The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

BMD Changes in Adolescent Females (12-18 years of age)

Preliminary results from an ongoing, open-label, self-selected, non-randomized clinical study of adolescent females (12-18 years) also showed that Depo-Provera CI use was associated with a significant decline in BMD from baseline (Table 3). In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density, with the result that they differed with respect to these demographic factors.

Preliminary data from the small number of adolescents participating in the 2-year post-use observation period demonstrated partial recovery of BMD.

Table 3. Mean Percent Change from Baseline in BMD in Adolescents by Skeletal Site and Cohort

| Duration of Treatment | Depo-Provera CI (150 mg IM) | | Unmatched, Untreated Cohort | |
|-------------------------|--------------------------------|---------------|--------------------------------|---------------|
| | N | Mean % Change | N | Mean % Change |
| Total Hip BMD | | | | |
| Week 60 (1.2 years) | 103 | -2.82 | 171 | 1.32 |
| Week 144 (2.8 years) | 45 | -6.16 | 111 | 1.74 |
| Week 240 (4.6 years) | 9 | -6.92 | 69 | 1.12 |
| Femoral Neck BMD | | | | |
| Week 60 | 103 | -3.05 | 171 | 1.87 |
| Week 144 | 45 | -6.01 | 111 | 2.54 |
| Week 240 | 9 | -6.06 | 69 | 1.45 |
| Lumbar Spine BMD | | | | |
| Week 60 | 104 | -2.42 | 171 | 3.47 |
| Week 144 | 46 | -2.78 | 111 | 5.41 |
| Week 240 | 9 | -4.17 | 70 | 5.12 |

2. Bleeding Irregularities

Most women using DEPO-PROVERA CI experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment should be instituted when necessary.

As women continue using DEPO-PROVERA CI, fewer experience irregular bleeding and more experience amenorrhea. By month 12 amenorrhea was reported by 55% of women, and by month 24 amenorrhea was reported by 68% of women using DEPO-PROVERA CI.²

3. Cancer Risks

Long-term case-controlled surveillance of users of DEPO-PROVERA CI found slight or no increased overall risk of breast cancer³ and no overall increased risk of ovarian,⁴ liver,⁵ or cervical⁶ cancer and a prolonged, protective effect of reducing the risk of endometrial⁷ cancer in the population of users.

A pooled analysis¹⁴ from two case-control studies, the World Health Organization Study³ and the New Zealand Study¹³, reported the relative risk (RR) of breast cancer for women who had ever used DEPO-PROVERA CI as 1.1 (95% confidence interval (CI) 0.97 to 1.4). Overall, there was no increase in risk with increasing duration of use of DEPO-PROVERA CI. The RR of breast cancer for women of all ages who had initiated use of DEPO-PROVERA CI within the previous 5 years was estimated to be 2.0 (95% CI 1.5 to 2.8).

The World Health Organization Study³, a component of the pooled analysis¹⁴ described above, showed an increased RR of 2.19 (95% CI 1.23 to 3.89) of breast cancer associated with use of DEPO-PROVERA CI in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall RR for ever-users of DEPO-PROVERA CI was only 1.2 (95% CI 0.96 to 1.52).

[NOTE: A RR of 1.0 indicates neither an increased nor a decreased risk of cancer associated with the use of the drug, relative to no use of the drug. In the case of the subpopulation with a RR of 2.19, the 95% CI is fairly wide and does not include the value of 1.0, thus inferring an increased risk of breast cancer in the defined subgroup relative to nonusers. The value of 2.19 means that women whose first exposure to drug was within the previous 4 years and who are under 35 years of age have a 2.19 fold (95% CI 1.23 to 3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer Institute⁸ reports an average annual incidence rate for breast cancer for US women, all races, age 30 to 34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible risk from 26.7 to 58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per 100,000 women per year.]

A statistically insignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of DEPO-PROVERA CI in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93 to 1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used DEPO-PROVERA CI was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in risk with duration of use or times since initial or most

recent exposure were observed.

4. *Thromboembolic Disorders*

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, the drug should not be readministered.

5. *Ocular Disorders*

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

6. *Unexpected Pregnancies*

To ensure that DEPO-PROVERA CI is not administered inadvertently to a pregnant woman, the first injection must be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, **ONLY** at the sixth postpartum week (see DOSAGE AND ADMINISTRATION).

Neonates from unexpected pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA CI 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.^{9,10}

A significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of DEPO-PROVERA CI, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptional exposure to DEPO-PROVERA CI, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.¹¹

Neonates 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.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (five to eight per 1,000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but because some of these drugs induce mild virilization of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

To ensure that DEPO-PROVERA CI is not administered inadvertently to a pregnant woman, it is important that the first injection be given only during the first 5 days after the onset of a normal menstrual period within 5 days postpartum if not breast-feeding and if breast-feeding, at the sixth week postpartum (see DOSAGE AND ADMINISTRATION).

7. Ectopic Pregnancy

Health-care providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA CI who become pregnant or complain of severe abdominal pain.

8. Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA CI. In nursing mothers treated with DEPO-PROVERA CI, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

9. Anaphylaxis and Anaphylactoid Reaction

Anaphylaxis and anaphylactoid reaction have been reported with the use of DEPO-PROVERA CI. If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

PRECAUTIONS

GENERAL

1. Physical Examination

It is good medical practice for all women to have annual history and physical examinations, including women using DEPO-PROVERA CI. The physical examination, however, may be deferred until after initiation of DEPO PROVERA CI if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Fluid Retention

Because progestational drugs may cause some degree of fluid retention, conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction, require careful observation.

3. Weight Changes

There is a tendency for women to gain weight while on therapy with DEPO-PROVERA CI. From an initial average body weight of 136 lb, women who completed 1 year of therapy with DEPO-PROVERA CI gained an average of 5.4 lb. Women who completed 2 years of therapy gained an average of 8.1 lb.

Women who completed 4 years gained an average of 13.8 lb. Women who completed 6 years gained an average of 16.5 lb. Two percent of women withdrew from a large-scale clinical trial because of excessive weight gain.

4. Return of Fertility

DEPO-PROVERA CI has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA CI to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the

duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA CI to become pregnant and who were lost to follow-up or changed their mind.

5. CNS Disorders and Convulsions

Patients who have a history of psychic depression should be carefully observed and the drug not be readministered if the depression recurs.

There have been a few reported cases of convulsions in patients who were treated with DEPO-PROVERA CI. Association with drug use or pre-existing conditions is not clear.

6. Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients on DEPO-PROVERA CI treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

7. Liver Function

If jaundice develops, consideration should be given to not readministering the drug.

8. Protection Against Sexually Transmitted Diseases

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DRUG INTERACTIONS

Aminoglutethimide administered concomitantly with the DEPO-PROVERA CI may significantly depress the serum concentrations of medroxyprogesterone acetate.¹² Users of DEPO-PROVERA CI should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

LABORATORY TEST INTERACTIONS

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

The following laboratory tests may be affected by progestins including DEPO-PROVERA CI:

- (a) Plasma and urinary steroid levels are decreased (eg, progesterone, estradiol, pregnanediol, testosterone, cortisol).
- (b) Gonadotropin levels are decreased.
- (c) Sex-hormone-binding-globulin concentrations are decreased.
- (d) Protein-bound iodine and butanol extractable protein-bound iodine may increase.
T₃-uptake values may decrease.
- (e) Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
- (f) Sulfobromophthalein and other liver function test values may be increased.
- (g) The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

CARCINOGENESIS

See "WARNINGS" section 3.

PREGNANCY

Pregnancy Category X. See “WARNINGS” section 6.

NURSING MOTHERS

See “WARNINGS” section 8.

PEDIATRIC USE

Depo-Provera CI is not indicated before menarche. Use of Depo-Provera CI is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. **In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.** It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

INFORMATION FOR THE PATIENT

See Patient Labeling.

Patient labeling is included with each single-dose vial and prefilled syringe of DEPO-PROVERA CI to help describe its characteristics to the patient. It is recommended that prospective users be given this labeling and be informed about the risks and benefits associated with the use of DEPO-PROVERA CI, as compared with other forms of contraception or with no contraception at all. It is recommended that physicians or other health-care providers responsible for those patients advise them at the beginning of treatment that their menstrual cycle may be disrupted and that irregular and unpredictable bleeding or spotting results, and that this usually decreases to the point of amenorrhea as treatment with DEPO-PROVERA CI continues, without other therapy being required.

ADVERSE REACTIONS

In the largest clinical trial with DEPO-PROVERA CI, over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA CI.

The following adverse reactions were reported by more than 5% of subjects:

Menstrual irregularities (bleeding or amenorrhea, or both)

Abdominal pain or discomfort

Weight changes

Dizziness

Headache

Asthenia (weakness or fatigue)

Nervousness

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA

Contraceptive Injection were:

Decreased libido or anorgasmia

Pelvic pain

Backache

Breast pain

Leg cramps

No hair growth or alopecia

Depression

Bloating

Nausea

Rash

Insomnia

Edema

Leukorrhea

Hot flashes

Acne

Arthralgia

Vaginitis

Events reported by fewer than 1% of subjects included: galactorrhea, melasma, chloasma, convulsions, changes in appetite, gastrointestinal disturbances, jaundice, genitourinary infections, vaginal cysts, dyspareunia, paresthesia, chest pain, pulmonary

embolus, allergic reactions, anemia, drowsiness, syncope, dyspnea and asthma, tachycardia, fever, excessive sweating and body odor, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical cancer, varicose veins, dysmenorrhea, hirsutism, unexpected pregnancy, thrombophlebitis, deep vein thrombosis.

Postmarketing Experience

There have been rare cases of osteoporosis including osteoporotic fractures reported postmarketing in patients taking Depo-Provera CI. In addition, there have been voluntary reports of anaphylaxis and anaphylactoid reaction associated with the use of Depo-Provera CI.

DOSAGE AND ADMINISTRATION

Both the 1 mL vial and the 1 mL prefilled syringe of DEPO-PROVERA CI should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of DEPO-PROVERA CI every 3 months (13 weeks) administered by deep, IM injection in the gluteal or deltoid muscle. To ensure the patient is not pregnant at the time of the first injection, the first injection **MUST** be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding; and if exclusively breast-feeding, **ONLY** at the sixth postpartum week. If the time interval between injections is greater than 13 weeks, the physician should determine that the patient is not pregnant before administering the drug. The efficacy of DEPO-PROVERA CI depends on adherence to the dosage schedule of administration.

HOW SUPPLIED

DEPO-PROVERA CI (medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL) is available as:

| | |
|------------------|------------------------------|
| NDC 0009-0746-30 | 1 mL vial |
| NDC 0009-0746-35 | 25 x 1 mL vials |
| NDC 0009-7376-01 | 1 mL prefilled syringe |
| NDC 0009-7376-02 | 6 x 1 mL prefilled syringes |
| NDC 0009-7376-03 | 24 x 1 mL prefilled syringes |

DEPO-PROVERA CI prefilled syringes are available packaged with 22-gauge x 1 1/2 inch BD SafetyGlide™ Needles in the following presentations:

| | |
|------------------|------------------------------|
| NDC 0009-7376-04 | 1 mL prefilled syringe |
| NDC 0009-7376-05 | 6 x 1 mL prefilled syringes |
| NDC 0009-7376-06 | 24 x 1 mL prefilled syringes |

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

REFERENCES

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Rx only

DEPO-PROVERA Contraceptive Injection 1 mL vials are manufactured by:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

DEPO-PROVERA Contraceptive Injection 1 mL prefilled syringes are manufactured
by:

Pharmacia & Upjohn, N.V./S.A.
Puurs, Belgium

for:

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

LAB-0149-2.1

Revised November 2004

Patient Labeling

Use of Depo-Provera Contraceptive Injection may cause you to lose calcium stored in your bones. The longer you use Depo-Provera Contraceptive Injection the more calcium you are likely to lose. The calcium may not return completely once you stop using Depo-Provera Contraceptive Injection.

Loss of calcium may cause weak, porous bones (osteoporosis) that could increase the risk that your bones might break, especially after menopause. It is not known whether your risk of developing osteoporosis may be greater if you are a teenager when you start to use Depo-Provera Contraceptive Injection.

You should use Depo-Provera Contraceptive Injection long term (for example, more than two years) only if other methods of birth control are not right for you. (See “Risks of Using Depo-Provera Contraceptive Injection”)

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Introduction

Every woman who considers using DEPO-PROVERA Contraceptive Injection needs to understand the benefits and risks of this form of birth control and to discuss them with her health-care provider. This leaflet is intended to give you much of the information you will need in order to decide if DEPO-PROVERA Contraceptive Injection is the right choice for you. Your health-care provider will help you to compare DEPO-PROVERA Contraceptive Injection with other contraceptive methods and will answer any questions you have after you have read this information.

DEPO-PROVERA Contraceptive Injection is given as an intramuscular injection (a shot) in the buttock or upper arm once every 3 months (13 weeks). Promptly at the end of the 3-month interval, you will need to return to your health-care provider for your next injection in order to continue your contraceptive protection.

DEPO-PROVERA Contraceptive Injection contains medroxyprogesterone acetate, a chemical similar to (but not the same as) the natural hormone progesterone that is produced by your ovaries during the second half of your menstrual cycle. DEPO-PROVERA Contraceptive Injection acts by preventing your egg cells from ripening. If an egg is not released from the ovaries during your menstrual cycle, it cannot become fertilized by sperm and result in pregnancy. DEPO-PROVERA Contraceptive Injection also causes changes in the lining of your uterus that make it less likely for pregnancy to occur.

Effectiveness of DEPO-PROVERA Contraceptive Injection

To ensure that DEPO-PROVERA Contraceptive Injection is not administered inadvertently to a pregnant woman, the first injection must be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not

breast-feeding, and if exclusively breast-feeding, **ONLY** at the sixth postpartum week (see **Administration of DEPO-PROVERA Contraceptive Injection**). The efficacy of DEPO-PROVERA Contraceptive Injection depends on adherence to the recommended dosage schedule.

DEPO-PROVERA Contraceptive Injection is over 99% effective, making it one of the most reliable methods of birth control available. This means that the average annual pregnancy rate is less than one for every 100 women who use DEPO-PROVERA Contraceptive Injection. The effectiveness of most contraceptive methods depends, in part, on how reliably each woman uses the method. The effectiveness of DEPO-PROVERA Contraceptive Injection depends only on the patient returning every 3 months (13 weeks) for her next injection.

The following table shows the percent of women who become pregnant while using different kinds of contraceptive methods. It gives both the lowest expected rate of pregnancy (the rate expected in women who use each method exactly as it should be used) and the typical rate of pregnancy (which includes women who became pregnant because they forgot to use their birth control or because they did not follow the directions exactly).

Percent of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

| Method | Lowest | Typical |
|-----------------------------|---------------|----------------|
| DEPO-PROVERA | 0.3 | 0.3 |
| Implants (Norplant) | 0.2* | 0.2* |
| Female sterilization | 0.2 | 0.4 |
| Male sterilization | 0.1 | 0.15 |
| Oral contraceptives (pill) | — | 3 |
| Combined | 0.1 | — |
| Progestogen only | 0.5 | — |
| IUD | — | 3 |
| Progestasert | 2 | — |
| Copper T 380A | 0.8 | — |
| Condom (without spermicide) | 2 | 12 |
| Diaphragm (with spermicide) | 6 | 18 |
| Cervical cap | 6 | 18 |
| Withdrawal | 4 | 18 |
| Periodic abstinence | 1-9 | 20 |
| Spermicide alone | 3 | 21 |
| Vaginal sponge | — | — |
| used before childbirth | 6 | 18 |
| used after childbirth | 9 | 28 |
| No method | 85 | 85 |

Source: Trussell et al; *Obstet Gynecol* 1990;76:558-567.

* From Norplant[®] package insert.

Who Should Not Use DEPO-PROVERA Contraceptive Injection

Certain women should not use DEPO-PROVERA Contraceptive Injection. You should not use DEPO-PROVERA Contraceptive Injection if you have any of the

following conditions:

- if you think you might be pregnant
- if you have any vaginal bleeding without a known reason
- if you have had cancer of the breast
- if you have had a stroke
- if you have or have had blood clots (phlebitis) in your legs
- if you have problems with your liver or liver disease
- if you are allergic to DEPO-PROVERA Contraceptive Injection (medroxyprogesterone acetate or any of its other ingredients)

Other Things to Consider Before Choosing DEPO-PROVERA Contraceptive Injection

Before your doctor prescribes DEPO-PROVERA Contraceptive Injection, you will have a physical examination. It is important to tell your doctor or health-care provider if you have any of the following:

- a family history of cancer of the breast
- an abnormal mammogram (breast X-ray), fibrocystic breast disease, breast nodules or lumps, or bleeding from your nipples
- kidney disease
- irregular or scanty menstrual periods
- high blood pressure
- migraine headaches
- asthma
- epilepsy (convulsions or seizures)
- diabetes or a family history of diabetes
- a history of depression
- if you are taking any prescription or over-the-counter medications

This product is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

Return of Fertility

Because DEPO-PROVERA Contraceptive Injection is a long-acting birth control method, it takes some time after your last injection for its effect to wear off. Based on the results from a large study done in the United States, of those women who stop using DEPO-PROVERA Contraceptive Injection in order to become pregnant, about half of those who become pregnant do so in about 10 months after their last injection; about two-thirds of those who become pregnant do so in about 12 months, about 83% of those who become pregnant do so in about 15 months, and about 93% of those who become pregnant do so in about 18 months after their last injection. The length of time you use DEPO-PROVERA Contraceptive Injection has no effect on how long it takes you to become pregnant after you stop using it.

Risks of Using DEPO-PROVERA Contraceptive Injection

1. Losing Calcium from Your Bones

Depo-Provera CI use may decrease the amount of calcium in your bones. The longer

you are on Depo-Provera CI the more calcium you may lose. This increases the risk of your bones weakening if you use Depo-Provera CI continuously for a long time (for more than 2 years). The loss of calcium may increase your risk of osteoporosis and broken bones, particularly after your menopause.

Calcium is generally added to the bones during teenage years. The decrease of calcium in your bones is of most concern if you are a teenager or have the following risk factors:

- bone disease
- anorexia nervosa (an eating disorder)
- a strong family history of osteoporosis
- drug use that can lower the amount of calcium in bones (drugs for epilepsy or steroids), or
- drinking a lot of alcohol or smoking a lot.

If you need a birth control method for more than 2 years, your healthcare provider may ask you to switch to another birth control method or ask you to have a test of your bones before continuing Depo-Provera CI, especially if you have other risks for weak bones. When Depo-Provera CI is stopped, the calcium in bones begins to come back. Your healthcare provider may tell you take calcium and Vitamin D as this may lessen the loss of calcium from your bones.

2. Irregular Menstrual Bleeding

The side effect reported most frequently by women who use DEPO-PROVERA Contraceptive Injection for contraception is a change in their normal menstrual cycle. During the first year of using DEPO-PROVERA Contraceptive Injection, you might have one or more of the following changes:

- irregular or unpredictable bleeding or spotting,
- an increase or decrease in menstrual bleeding, or
- no bleeding at all.

Unusually heavy or continuous bleeding, however, is not a usual effect of DEPO-PROVERA Contraceptive Injection and if this happens you should see your health-care provider right away.

With continued use of DEPO-PROVERA Contraceptive Injection, bleeding usually decreases and many women stop having periods completely. In clinical studies of DEPO-PROVERA Contraceptive Injection, 55% of the women studied reported no menstrual bleeding (amenorrhea) after 1 year of use and 68% of the women studied reported no menstrual bleeding after 2 years of use.

The reason that your periods stop is because DEPO-PROVERA Contraceptive Injection causes a resting state in your ovaries. When your ovaries do not release an egg monthly, the regular monthly growth of the lining of your uterus does not occur and, therefore, the bleeding that comes with your normal menstruation does not take place. When you stop using DEPO-PROVERA Contraceptive Injection your menstrual period will usually, in time, return to its normal cycle.

3. Cancer

Studies of women who have used different forms of contraception found that women who used DEPO-PROVERA Contraceptive Injection for contraception had no increased overall risk of developing cancer of the breast, ovary, uterus, cervix, or liver. However,

women under 35 years of age whose first exposure to DEPO-PROVERA Contraceptive Injection was within the previous 4 to 5 years may have a slightly increased risk of developing breast cancer similar to that seen with oral contraceptives. You should discuss this with your health-care provider.

4. Unexpected Pregnancy

Because DEPO-PROVERA Contraceptive Injection is such an effective contraceptive method, the risk of unexpected pregnancy for women who get their shots regularly (every 3 months [13 weeks]) is very low. While there have been reports of an increased risk of low birth weight and neonatal infant death or other health problems in infants conceived close to the time of injection, such pregnancies are uncommon. If you think you may have become pregnant while using DEPO-PROVERA Contraceptive Injection for contraception, see your health-care provider as soon as possible.

5. Allergic Reactions

Severe allergic reactions known as anaphylaxis and anaphylactoid reactions have also been reported in some women using DEPO-PROVERA Contraceptive Injection.

6. Other Risks

Women who use hormone-based contraceptives may have an increased risk of blood clots or stroke. Also, if a contraceptive method fails, there is a possibility that the fertilized egg will begin to develop outside of the uterus (ectopic pregnancy). While these events are rare, you should tell your health-care provider if you have any of the Warning Signals listed in the next section.

Warning Signals

If any of these problems occur following an injection of DEPO-PROVERA Contraceptive Injection, call your healthcare provider immediately:

- Sharp chest pain, coughing up of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Sudden severe headache or vomiting, dizziness or fainting, problems with your eyesight or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Severe pain or swelling in the calf (indicating a possible clot in the leg)
- Unusually heavy vaginal bleeding
- Severe pain or tenderness in the lower abdominal area
- Persistent pain, pus, or bleeding at the injection site

Side Effects of DEPO-PROVERA Contraceptive Injection

1. Weight Gain

You may experience a weight gain while you are using DEPO-PROVERA Contraceptive Injection. About two-thirds of the women who used DEPO-PROVERA Contraceptive Injection in the clinical trials reported a weight gain of about 5 pounds during the first year of use. You may continue to gain weight after the first year. Women in one large study who used DEPO-PROVERA Contraceptive Injection for 2 years gained an average total of 8.1 pounds over those 2 years, or approximately 4 pounds per year. Women who continued for 4 years gained an average total of 13.8 pounds over those 4 years, or approximately 3.5 pounds per year. Women who continued for 6 years gained an average total of 16.5 pounds over those 6 years, or approximately 2.75 pounds per year.

2. Other Side Effects

In a clinical study of over 3,900 women who used DEPO-PROVERA Contraceptive Injection for up to 7 years, some women reported the following effects that may or may not have been related to their use of DEPO-PROVERA Contraceptive Injection:

- irregular menstrual bleeding
- amenorrhea
- headache
- nervousness
- abdominal cramps
- dizziness
- weakness or fatigue
- decreased sexual desire
- leg cramps
- nausea
- vaginal discharge or irritation
- breast swelling and tenderness
- bloating
- swelling of the hands or feet
- backache
- depression
- insomnia
- acne
- pelvic pain
- no hair growth or excessive hair loss
- rash
- hot flashes
- joint pain

Other problems were reported by very few of the women in the clinical trials, but some of these could be serious. These include: convulsions, jaundice, urinary tract infections, allergic reactions, fainting, paralysis, osteoporosis, lack of return to fertility, deep vein thrombosis, pulmonary embolus, breast cancer, or cervical cancer. If these or any other problems occur during your use of DEPO-PROVERA Contraceptive Injection, discuss them with your health-care provider.

General Precautions

1. Missed Periods

During the time you are using DEPO-PROVERA Contraceptive Injection for contraception, you may skip a period, or your periods may stop completely. If you have been receiving your injection of DEPO-PROVERA Contraceptive Injection regularly every 3 months (13 weeks), then you are probably not pregnant. However, if you think that you may be pregnant, see your health-care provider.

2. Laboratory Test Interactions

If you are scheduled for any laboratory tests, tell your health-care provider that you are using DEPO-PROVERA Contraceptive Injection for contraception. Certain blood tests are affected by hormones such as DEPO-PROVERA Contraceptive Injection.

3. Drug Interactions

Cytadren (aminoglutethimide) is an anticancer drug that may significantly decrease the effectiveness of DEPO-PROVERA Contraceptive Injection if the two drugs are given during the same time.

4. Nursing Mothers

Although DEPO-PROVERA Contraceptive Injection can be passed to the nursing infant in the breast milk, no harmful effects have been found in these children. DEPO-PROVERA Contraceptive Injection does not prevent the breasts from producing milk, so it can be used by nursing mothers. However, to minimize the amount of DEPO-PROVERA Contraceptive Injection that is passed to the infant in the first weeks after

birth, you should wait until 6 weeks after childbirth before you start using DEPO-PROVERA Contraceptive Injection for contraception.

Administration of DEPO-PROVERA Contraceptive Injection

The recommended dose of DEPO-PROVERA Contraceptive Injection is 150 mg every 3 months (13 weeks) given in a single intramuscular injection in the buttock or upper arm. To ensure that you are not pregnant at the time of the first injection, it is essential that the injection be given **ONLY** during the first 5 days of a normal menstrual period. If used following the delivery of a child, the first injection of DEPO-PROVERA Contraceptive Injection **MUST** be given within 5 days after childbirth if you are not breast-feeding, or if you are exclusively breast-feeding, the injection **MUST** be given 6 weeks after childbirth. If you wait longer than 3 months (13 weeks) between injections, or longer than 6 weeks after delivery, your health-care provider should determine that you are not pregnant before giving you your injection of DEPO-PROVERA Contraceptive Injection.

Rx only

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA
Revised October 2004

815 463 612

692819

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020246Orig1s025

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type 20-246
Submission Number 025
Submission Code CBE SLR

Letter Date 8Sep2004
Stamp Date 8Sep2004

Reviewer Name L. Furlong
Review Completion Date 22Sep2004

Established Name medroxyprogesterone acetate
Trade Name Depo-Provera Contraceptive
Injection
Therapeutic Class contraceptives/not oral
Applicant Pfizer

Priority Designation S

Formulation Suspension
Dosing Regimen Intramuscular injection every 3
months
Indication Prevention of pregnancy
Intended Population Women of reproductive age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of the proposed labeling changes if the Applicant agrees to several minor edits.

1.2.2 Required Phase 4 Commitments

The Applicant should commit to updating the section of the label related to bone mineral density changes when the final study report for Study 261, a seven-year observational study of BMD in adolescents using DMPA, becomes available.

2 INTRODUCTION AND BACKGROUND

Pfizer is upgrading the safety labeling regarding effects of Depo-Provera Contraceptive Injection on bone mineral density (BMD) to reflect a recent analysis of data from postmarketing safety studies, reviewed by FDA for a related new drug application (NDA 21-583). In addition, Pfizer provided a summary of postmarketing reports related to bone fracture and osteoporosis to support the addition of a postmarketing section in the adverse reactions section of the label.

The wording that Pfizer used to update the BMD section was recommended by the FDA in the labeling negotiations for NDA 21-583 with a few exceptions. The submission also includes comments to support these exceptions.

Other changes include replacing

- "Contraceptive Injection" with "CI"
- (b) (4) with an alpha in the chemical name.
- The contraindication "Liver disease" with (b) (4) liver disease.

The downgraded contraindication regarding liver disease was provided without comment.

In addition, Pfizer states in the cover letter for the submission that "Pfizer intends to provide details regarding the labeling update via a Dear Healthcare Professional Letter." A draft of the letter was not provided in the submission.

For ease of review, this reviewer's comments are inserted following the corresponding changes in the label that is reproduced in Section 9.4.

9 OVERALL ASSESSMENT

9.4 Labeling Review

Overall, the changes were acceptable. For the Package Insert, I recommend a few minor spelling and formatting changes, and these are shown in the Appendix (See page 7.) My additions are highlighted in yellow and underlined, and deletions are marked with single strikeout. Minor formatting changes are not shown. A brief summary of changes related to the Package Insert, along with my comments about the changes, is in the next subsection.

(The changes in the Patient Package Insert were consistent with the Package Insert. My recommendations for the Patient Package Insert are minor, and are not reproduced in this review.)

Summary of Pfizer's Changes and Reviewer's Comments Regarding Package Insert

Lines 2 to 12: Pfizer has added a boxed warning. The first 2 paragraphs are taken verbatim from FDA recommendations for NDA 21-583. [REDACTED] (b) (4) the last paragraph is taken verbatim from FDA recommendations for a statement in Warnings. It is acceptable to place it here.

Line 19: Pfizer is abbreviating "Contraceptive Injection" with CI. Although CI is sometimes used to mean "confidence interval", the context should make it clear.

Line 27: Change from [REDACTED] (b) (4) to alpha acceptable to FDA chemistry reviewer because the change is consistent with the name provided in the USP.

Lines 63 to 67: The added sentence is taken verbatim from FDA recommendations for the label for DMPA-SC (NDA 21-583), and is acceptable.

Line 107: Pfizer did not provide any support for the change from "Liver dysfunction" to [REDACTED] (b) (4) liver dysfunction". The change is similar to current recommendations from the World Health Organization (WHO), which recommends against use in cases of "severe (decompensated) cirrhosis" and "active viral hepatitis". However, WHO is silent on the use of Depo-Provera in cases of moderate cirrhosis. The single published study that I was able to find evaluated 25 subjects with liver dysfunction and concluded that medroxyprogesterone acetate elimination is impaired only in cases with far advanced liver disease. (The abstract is included in the Appendix. See page 32.) Pfizer has no formal studies of Depo-Provera Contraceptive Injection in hepatic dysfunction, but there is evidence that medroxyprogesterone acetate is extensively metabolized by the liver. [REDACTED] (b) (4)

[REDACTED] I would prefer the term "significant", to leave it to the clinician's discretion to prescribe in cases where there are mild elevations of liver enzymes, for example.

Lines 112-167: This section is almost verbatim with FDA recommendations. Differences include

[REDACTED] (b) (4)

[REDACTED] (b) (4) Pfizer reasonably argues that the control group was different from the treatment group in ways that exaggerate the difference in BMD. That is, the control group was older, more likely to be African-American, had a higher prevalence of smoking (10X), and had an earlier age of menarche. [REDACTED] (b) (4) I recommend that Pfizer consider

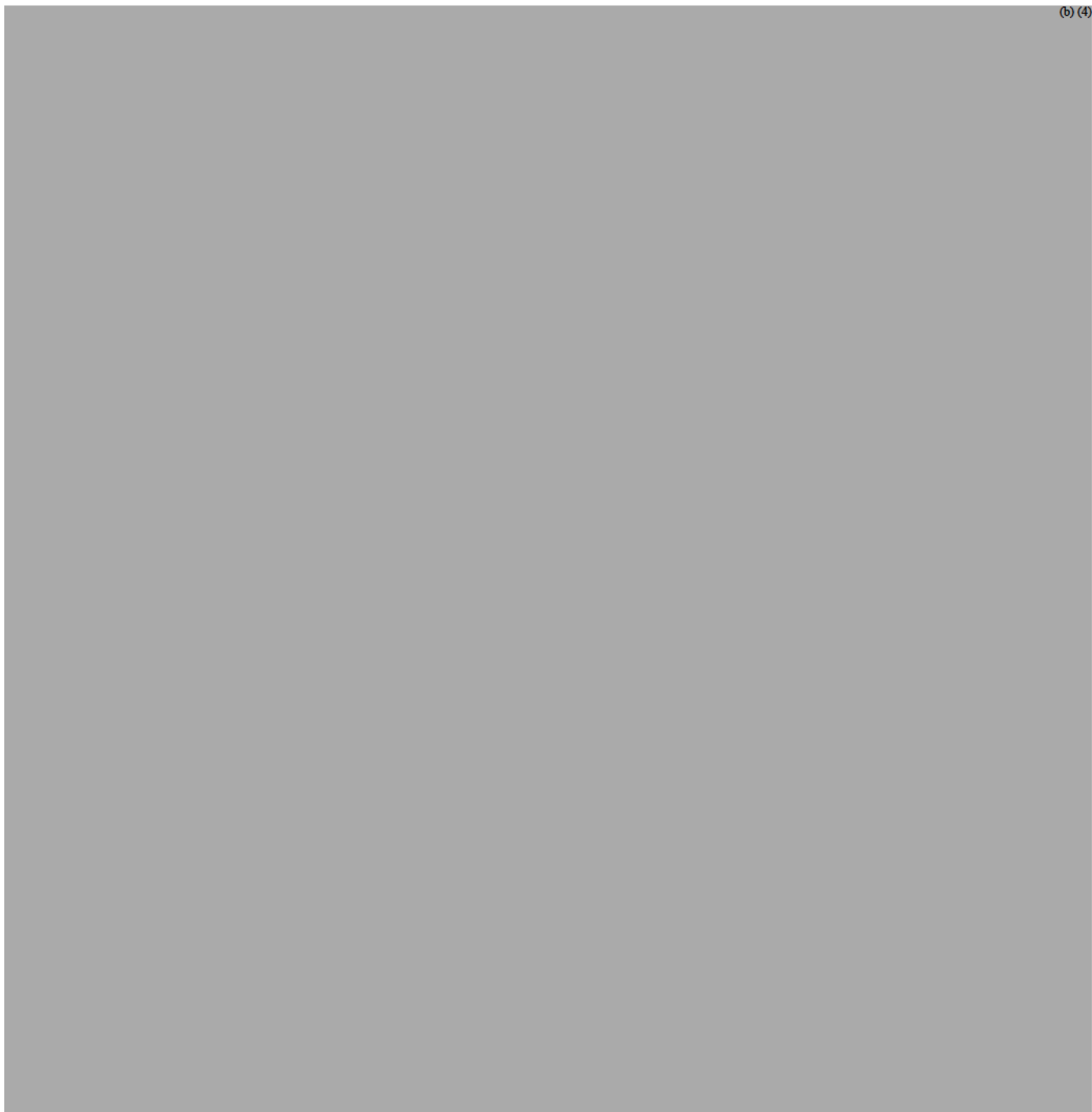
an analysis of variance using years since menarche and other significant variables when they prepare the final study report. (b) (4)

Lines 354 to 363: Changes in the PEDIATRIC USE Section come verbatim from FDA recommendations for NDA 21-583, except for the addition of the bolded sentence. The addition is acceptable.

Lines 419 to 424: The inclusion of a subsection called Postmarketing Experience to the label was based on the Applicant's analysis of postmarketing reports. The addition is acceptable.

10 APPENDICES

10.2 Line-by-Line Labeling Review



BACKGROUND MATERIAL TO SUPPORT CHANGE IN CONTRAINDICATION RELATED TO LIVER DISEASE

Medical Eligibility Criteria for Contraceptive Use – World Health Organization (WHO),
Third Edition 2004

The following two tables were adapted from the WHO Medical Criteria for Contraceptive Use, and are consistent with the change from "Liver dysfunction" to ^{(b) (4)} liver dysfunction" in the Contraindications Section of the label. This 2004 recommendation from WHO does *not* represent a change from previous WHO recommendations.

WHO Categories for Contraceptive Use

| <i>CATEGORY</i> | <i>WITH CLINICAL JUDGEMENT</i> |
|-----------------|---|
| 1 | Use method in any circumstances |
| 2 | Generally use the method |
| 3 | Use of method not usually recommended unless other more appropriate methods are not available or not acceptable |
| 4 | Method not to be used |

WHO Medical Eligibility Criteria for Depo-Provera Contraceptive Injection Related to Cholestasis, Hepatitis and Cirrhosis

| <i>HISTORY OF CHOLESTASIS</i> | |
|-------------------------------|---|
| a) Pregnancy-related | 1 |
| b) Past COC-related | 2 |
| <i>VIRAL HEPATITIS</i> | |
| a) Active | 3 |
| b) Carrier | 1 |
| <i>CIRRHOSIS</i> | |
| a) Mild (compensated) | 2 |
| b) Severe (decompensated) | 3 |

Liver function and medroxyprogesterone acetate elimination in man.

Biomed Pharmacother. 1984;38(4):199-204

Rautio A.

Medroxyprogesterone acetate (MPA) elimination rate was investigated in 25 patients with primary biliary cirrhosis, alcoholic cirrhosis and fatty liver. The serum and urine concentrations of MPA were measured by RIA after a single oral administration of the drug. Biochemical liver tests and antipyrine kinetics were determined as indicators of the liver function. The antipyrine test, a reflector of the activity of hepatic drug-metabolizing enzyme system, was impaired only in alcoholics. The results demonstrate that the elimination rate of MPA is reduced in subjects with alcoholic cirrhosis, whereas the values of the patients with fatty liver and primary biliary cirrhosis are in the normal range. The findings show that the MPA elimination is impaired only in cases with far advanced liver disease.

PMID: 6498308 [PubMed - indexed for MEDLINE]

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this page is the manifestation of the electronic signature.**

/s/

Leslie Ann Furlong
12/7/04 07:49:06 AM
MEDICAL OFFICER

Scott Monroe
12/7/04 09:05:46 PM
MEDICAL OFFICER

I concur with the recommendations of Dr. Furlong with
the exception that (b)(4)

[REDACTED]

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
020246Orig1s025

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM OF TELECON

DATE: April 8, 2005

APPLICATION NUMBER: NDAs 20-246/21-583/21-584

BETWEEN:

Name: Jennifer Bingaman, Manager Worldwide Regulatory Strategy

Phone: 212-733-0098

Representing: Pfizer Global Pharmaceuticals

AND

Name: Margaret Kober, R.Ph., Chief, Project Management Staff

Charlene Williamson, Project Manager

Division of Reproductive and Urologic Drug Product, HFD-580

SUBJECT: To provide clarification to the sponsor concerning labeling submissions.

In December 17, 2004, Pfizer was issued an approval letter for depo-subQ provera 104™, NDA 21-583. In the March 7, 2005 submission, the sponsor submitted Final Printed Labeling (FPL) with revisions. The sponsor was informed that FPL must be identical to what was approved and the submission would be changed to a supplement to incorporate the changes. The same drug product was also approved under NDA 21-584 in March 2005 for an additional indication. Once the sponsor submits the dual indication FPL to NDA 21-584 and it is approved, a supplement should be submitted to NDA 21-583 incorporating the dual indication into the labeling. An FPL submission to 21-583 is required after approval of the dual indication labeling supplement.

Additionally, on February 10, 2005, the sponsor submitted labeling supplement NDA 20-246/S-027 which consisted of a revised patient brochure to incorporate changes consistent with those to the physician and patient inserts approved in November 2004 under NDA 20-246/S-025.

The submission is also intended to incorporate changes referenced in the November 1999 approvable letter issued for S-013. The February submission was changed to an amendment for to S-013. The sponsor was informed to submit the missing items (physician package insert and patient insert) to complete the response to the approvable letter for S-013. An additional FPL submission is required for S-013 upon approval. An FPL submission for supplement S-025 is still pending as well.

The sponsor agreed with our decisions and will submit the required labeling to complete the labeling deficiencies.

Charlene Williamson
Project Manager

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this page is the manifestation of the electronic signature.**

/s/

Z. Charlene Williamson
4/12/05 04:02:17 PM
CSO

Margaret Kober
4/18/05 02:12:25 PM
CSO

MEMO

DATE: 11/16/2004

TO: FILE FOR NDA 20-246 N025

CC: DONNA GRIEBEL, MD, DRUDP DEPUTY DIVISION DIRECTOR
SCOTT MONROE, MD, DRUDP TEAM LEADER
CHARLENE WILLIAMSON, PROJECT MANAGER

FROM: LESLEY FURLONG, MD

RE: UPDATED LABELING REGARDING BONE MINERAL DENSITY EFFECTS OF DEPO-PROVERA CONTRACEPTIVE INJECTION

This memo updates my review of Pfizer's proposed labeling changes for Depo-Provera Contraceptive Injection. Labeling negotiations were concluded satisfactorily in a teleconference between FDA and the Pfizer on 1-Nov-2004. Pfizer submitted final labeling on 4-Nov-2004. I reviewed the final labeling, found that it contains the agreed-upon text, and recommend approval.

The discussion during labeling negotiations focused on how to present the bone mineral density data for adolescents from ongoing Study 261. The study is nonrandomized, and the treatment and control groups are different in ways that impact bone mineral density. Both FDA and Pfizer agreed that the data should be presented with the caveat that the groups were not matched. Other changes included minor edits to clarify text. The label may need to be updated with the final results of Study 261 become available.

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/s/

Leslie Ann Furlong
11/16/04 11:45:42 AM
MEDICAL OFFICER



NDA 20-246/S-025

Pfizer, Global Pharmaceutical
Attention: Alan Traettino
US Regulatory Affairs
235 East 42nd Street 150/7/16
New York, NY 10017

CBE-30/CBE-0 SUPPLEMENT

Dear Mr. Traettino:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|-----------------------|--|
| Name of Drug Product: | Depo-Provera [®] Contraceptive Injection (medroxyprogesterone acetate injectable suspension) 150 mg/ml IM |
| NDA Number: | 20-246 |
| Supplement number: | 025 |
| Date of supplement: | September 8, 2004 |
| Date of receipt: | September 9, 2004 |

This supplemental application, submitted as "Supplement - Changes Being Effectuated in 30 days," proposes the following changes: for the addition of a Black Box Warning plus recommended text in the Indications and Usage and Warning sections concerning loss bone mineral density.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive, HFD-580
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph
Chief, Regulatory Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
9/27/04 08:54:55 AM
Chief, Project Management Staff



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2004

| | |
|--|--|
| To: Alan Traettino | From: Charlene Williamson Regulatory Project Manager |
| Company: Pfizer Pharmaceuticals Group | Division of Reproductive and Urologic Drug Products |
| Fax number: 212-672-7862 | Fax number: 301-827-4267 |
| Phone number: 212-733-7200 | Phone number: 301-827-4260 |
| Subject: CBE-30 | |

Total no. of pages including cover: 2

Comments: Please respond to this request by September 27, 2004

Document to be mailed: • YES NO

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To help us review your labeling changes, please confirm that:

Your document labeled "cleanphysician.doc" is the current package insert.

Your document labeled "revisedphysician.doc" shows your proposed changes to the current package insert.

By accepting all changes in the "revisedphysician.doc", we can produce a clean copy of your proposed package insert.

Your document labeled "cleanpatient.doc" is the current patient package insert.

Your document labeled "revisedpatient.doc" shows your proposed changes to the current patient package insert.

By accepting all changes in the "revisedpatient.doc", we can produce a clean copy of your proposed patient package insert.

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/s/

Z. Charlene Williamson
9/22/04 01:26:24 PM
CSO

Leslie Ann Furlong
9/22/04 03:29:34 PM
MEDICAL OFFICER