DEPO-PROVERA

medroxyprogesterone acetate

150 mg suspension for injection

Reference label: CDS

AfME markets using the same LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEPO-PROVERA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injectable suspension

Depot-medroxyprogesterone acetate (DEPO-PROVERA) injectable suspension is available in vials as 500 mg/3.3 mL.

3. PHARMACEUTICAL FORM

Injectable: Suspension for intramuscular (IM) injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Contraception
Depo-Provera injectable suspensions (IM) are indicated for:
- Contraception

Gynecology
Depo-Provera injectable IM suspension is indicated for:
- Treatment of endometriosis

Depo-Provera injectable IM suspension is indicated for:
- Treatment of menopausal vasomotor symptoms

Oncology
Depo-Provera injectable IM suspension is indicated for:
- Recurrent and/or metastatic breast cancer
- Recurrent and/or metastatic endometrial cancer
- Recurrent and/or metastatic renal cancer

Long-term Use
Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use Depo-Provera injection long-term (**see Section 4.4. Special warnings and precautions for use - Additional Warnings and Precautions for Specific Use or Formulation, *Contraception/Endometriosis - Injectable Formulations*:** Loss of Bone Mineral Density and **Section 5.1. Pharmacodynamic properties - *Clinical Studies*,** Bone Mineral Density Studies), 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 Children
Depo-Provera IM is not indicated before menarche. Data are available in adolescent females (12-18 years) (**see Section 5.1. Pharmacodynamic properties - *Clinical Studies*,** *BMD Changes in Adolescent Females (12-18 years)*. The safety and effectiveness of Depo-Provera IM are expected to be the same for postmenarcheal adolescent and adult females.

4.2 Posology and method of administration

Injectable suspensions should be shaken well before use.

Contraception
Depo-Provera intramuscular (IM) injectable suspensions should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

Intramuscular (IM)
The recommended dose is 150 mg of Depo-Provera injectable suspension every 3 months (12-13 weeks) administered by intramuscular injection in the gluteal or deltoid muscle. The IM suspension is not formulated for subcutaneous injection.

First injection
The initial IM injection should be given during the first 5 days after the onset of a normal menstrual period; within 5 days postpartum if not breast-feeding; or, if exclusively breast-feeding, at or after 6 weeks postpartum.

Second and subsequent injections
If the time interval between IM injections is greater than 13 weeks, pregnancy should be ruled out before administering the next IM injection.

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

Gynecology
Use of combined estrogen/progestin therapy in postmenopausal women should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated. (**see Section 4.4 – Special warnings and precautions for use.**)

Periodic check-ups are recommended with a frequency and nature adapted to the individual woman. (**see Section 4.4 – Special warnings and precautions for use**.)

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestin in a woman without an intact uterus.

Endometriosis
- Injectable Depo-Provera, given intramuscularly 50 mg weekly or 100 mg every 2 weeks for at least 6 months.

Menopausal Vasomotor Symptoms
- Injectable Depo-Provera given intramuscularly 150 mg every 12 weeks.

Oncology

Recurrent and/or Metastatic Breast Cancer
- Injectable Depo-Provera initial dose 500 to 1000 mg intramuscularly per day for 28 days. The patient should then be placed on a maintenance schedule of 500 mg twice weekly as long as she responds to treatment.

Recurrent and/or Metastatic Endometrial or Renal Cancer

- Injectable Depo-Provera 400 to 1000 mg intramuscularly per week is recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month.

Hepatic Insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of Depo-Provera. However, Depo-Provera is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolized in patients with severe liver insufficiency (**see Section 4.3. Contraindications**).

Renal Insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of Depo-Provera. However, since Depo-Provera is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

4.3 Contraindications

Depo-Provera is contraindicated in patients with the following conditions:

- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction
- Known hypersensitivity to Depo-Provera or any component of the drug

Additional Contraindication(s) for Specific Use

Contraception/Gynecology: Known or suspected malignancy of the breast

4.4 Special warnings and precautions for use

General

- Unexpected vaginal bleeding during therapy with Depo-Provera should be investigated.
- Depo-Provera may cause some degree of fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving Depo-Provera therapy.
- Some patients receiving Depo-Provera may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.
- The pathologist (laboratory) should be informed of the patient's use of Depo-Provera if endometrial or endocervical tissue is submitted for examination.
- The physician/laboratory should be informed that use of Depo-Provera may decrease the levels of the following endocrine biomarkers:
    a. Plasma/urinary steroids (e.g., cortisol, estrogen, pregnanediol, progesterone, testosterone)
    b. Plasma/urinary gonadotrophins (e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
    c. Sex hormone-binding-globulin
- 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 papilloedema or retinal vascular lesions, medication should not be readministered.
- Depo-Provera has not been causally associated with the induction of thrombotic or thromboembolic disorders, however, Depo-Provera is not recommended in any patient with a history of venous

thromboembolism (VTE). Discontinuation of DEPO-PROVERA is recommended in patients who develop VTE while undergoing therapy with DEPO-PROVERA.

- Meningiomas have been reported following long term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Additional Warnings and Precautions for Specific Use or Formulation

Contraception/Endometriosis – Injectable Formulations

Loss of Bone Mineral Density (BMD)
Use of DEPO-PROVERA injection reduces serum estrogen levels in premenopausal women and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of DEPO-PROVERA injection during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females , the decrease in BMD during treatment appears to be substantially reversible after DEPO-PROVERA injection is discontinued and ovarian estrogen production increases (see **Section 5.1 – Pharmacodynamic Properties, *Clinical Studies,*** BMD Studies). After discontinuing Depo-Provera injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck (see **Section 5.1 – Pharmacodynamic Properties, *Clinical Studies,*** BMD Studies - BMD recovery post-treatment in adolescent women).

In adults, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see **Section 5.1 – Pharmacodynamic Properties, *Clinical Studies,*** BMD Studies - BMD Changes in Adult Women). A large observational study of female contraceptive users showed that use of Depo-Provera injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures (see **Section 5.1 – Pharmacodynamic Properties, *Clinical Studies,*** BMD Studies - Relationship of fracture incidence to use of DEPO-PROVERA injectable (150 mg IM) or non-use by women of reproductive age).

BMD Changes in Adult Women after Six Months of Treatment for Endometriosis
In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of DEPO-PROVERA SC treatment were Compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months.

The proportion of patients with a decrease of 5% or more in BMD was statistically significantly greater in the leuprolide group Compared with DEPO-PROVERA-SC at each time point (Table 1).

Table 1. Proportion of Patients with a Decrease of 5% or More from Baseline after 6 Months on Therapy with DEPO-PROVERA-SC or Leuprolide and 6 Months after Stopping Therapy (Studies 268 and 270 Combined)

BMD Parameter	DEPO-PROVERA-SC n/N* (%)	Leuprolide n/N* (%)	p-value**
End of Treatment (6 Months of Therapy)			
Spine	12/208 (5.8%)	85/229 (37.1%)	<0.001
Total Hip	1/207 (0.5%)	25/227 (11.0%)	<0.001
At 12 Month Visit (6 Months Off-Therapy)			
Spine	8/166 (4.8%)	32/178 (18.0%)	<0.001
Total Hip	3/166 (1.8%)	25/178 (14.0%)	<0.001

* n=number of patients with a decrease in BMD ≥5%; N=total observations
** chi-square

Other birth control methods or endometrial treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA injection in women with osteoporotic risk factors such as:

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

It is recommended that all patients have adequate calcium and Vitamin D intake.

Contraception

- Most women using DEPO-PROVERA injectable suspension experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding). As women continue using DEPO-PROVERA injectable suspension, fewer experience irregular bleeding and more experience amenorrhoea.
- Long-term case-controlled surveillance of users of DEPO-PROVERA injectable suspension found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer.
- DEPO-PROVERA IM injectable suspension has a prolonged contraceptive effect. The median time to contraception following the last injection, for those who do conceive, is 10 months, with a range of 4 to 31 months, and is unrelated to the duration of use.
  There was a tendency for women to gain weight while on therapy with DEPO-PROVERA.
- If jaundice develops, consideration should be given to not readminister the drug.

Sexually Transmitted Infections

Women should be counseled that DEPO-PROVERA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DEPO-PROVERA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Breast Cancer

See below.

Gynecology

Treatment of Menopausal Vasomotor Symptoms/Opposition of Endometrial Effects of Estrogen in Menopausal Women Being Treated with Estrogen (Hormone Therapy)-All Formulations:

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of Hormone Therapy (HT) were not studied in the Women's Health Initiative (WHI) trial (**see Section 5.1 – Pharmacodynamic Properties, *Clinical Studies*,** Women's Health Initiative Study) and, in the absence of comparable data, these risks should be assumed to be similar.

Breast Cancer

The use of combined oral estrogen/progestin by postmenopausal women has been reported to increase the risk of breast cancer. Results from a randomized placebo-controlled trial, the WHI trial, and epidemiological studies (**see Section 5.1 - Pharmacodynamic properties, *Clinical Studies***) have reported an increased risk of breast cancer in women taking estrogen/progestin combinations for HT for several years. In the WHI conjugated equine estrogens (CEE) plus DEPO-PROVERA trial and observational studies, the excess risk increased with duration of use (**see Section 4.2 - Posology and method of administration**). The use of estrogen plus progestin has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

In several epidemiologic studies no overall increased risk for breast cancer was found among users of injectable depot progestogens in comparison to non-users. However, an increased relative risk (e.g. 2.0 in one study) was found for women who currently used injectable depot progestogens or had used them only a few years before. It is not possible to infer from these data whether this increased rate of breast cancer diagnosis among current users is due to increased surveillance among current users, the biological effects of injectable progestogens, or a combination of reasons.

Cardiovascular Disorders

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. Several randomized, prospective trials on the long-term effects **(see Section 4.2. Posology and method of administration**), of a combined estrogen/progestin regimen in postmenopausal women have reported an increased risk of cardiovascular events such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.

- Coronary Artery Disease

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogen and medroxyprogesterone acetate (DEPO-PROVERA). Two large clinical trials [WHI CEE/DEPO-PROVERA and Heart and Estrogen/progestin Replacement Study (HERS) (**see Section 5.1 - Pharmacodynamic properties, *Clinical Studies***) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

In the WHI CEE/DEPO-PROVERA trial, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CEE/DEPO-PROVERA compared to women receiving placebo (37 vs. 30 per 10,000 person years). The increase in VTE risk was observed in year one and persisted over the observation period (**see Section 4.2 – Posology and method of administration**).

- Stroke

In the WHI CEE/DEPO-PROVERA trial, an increased risk of stroke was observed in women receiving CEE/DEPO-PROVERA compared to women receiving placebo (29 vs. 21 per 10,000 person-years). The increase in risk was observed in year one and persisted over the observation period (**see Section 4.2 - Posology and method of administration**).

- Venous thromboembolism / Pulmonary embolism

HT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. In the WHI CEE/DEPO-PROVERA trial, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism was observed in women receiving CEE/DEPO-PROVERA compared to women receiving placebo. The increase in

risk was observed in year one and persisted over the observation period (**see Section 4.4-Special warnings and precautions for use**).

Dementia
The Women's Health Initiative Memory Study (WHIMS) (**see Section 5.1 Pharmacodynamic Properties - *Clinical Studies***), an ancillary study of WHI, CEE/DEPO-PROVERA reported an increased risk of probable dementia in postmenopausal women 65 years of age or older. In addition, CEE/DEPO-PROVERA therapy did not prevent mild cognitive impairment (MCI) in these women. Use of hormone therapy (HT) to prevent dementia or MCI in women 65 years or older is not recommended.

Ovarian Cancer
Current use of estrogen only or estrogen plus progestin products in post-menopausal women for five or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. **[110]** Past users of estrogen only or estrogen plus progestin products were at no increased risk for ovarian cancer. **[110]** Other studies did not show a significant association. The WHI CEE/DEPO-PROVERA trial reported that estrogen plus progestin increased the risk of ovarian cancer, but this risk was not statistically significant. In one study, women who use HRT are at increased risk of fatal ovarian cancer.

History and Physical Exam Recommendation
A complete medical and family history should be taken before the initiation of any hormone therapy. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

Gynecology-Injectable Formulations
- Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of DEPO-PROVERA.

Oncology
- DEPO-PROVERA may produce Cushingoid symptoms.
- Some patients receiving DEPO-PROVERA may exhibit suppressed adrenal function. DEPO-PROVERA may decrease ACTH and hydrocortisone blood levels.
- The physician/laboratory should be informed that in addition to the endocrine biomarkers listed in **Section 4.4. Special warnings and precautions for use**, the use of DEPO-PROVERA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.

Oncology-Injectable Formulations
- Prolonged anovulation with amenorrhoea and/or erratic menstrual patterns may follow the administration of either a single or multiple injectable dose of DEPO-PROVERA.

High Dose Parenteral Formulations (e.g., oncology use in pre-menopausal women)

Decrease in Bone Mineral Density
There are no studies on the bone mineral density (BMD) effects of orally administered DEPO-PROVERA or the high doses of parenteral DEPO-PROVERA (e.g., for oncology use). An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term , (**see above – Loss of Bone Mineral Density**).

4.5 Interaction with other medicinal products and other forms of interaction

Medroxyprogesterone acetate (DEPO-PROVERA) 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 DEPO-PROVERA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Pregnancy and lactation

Pregnancy

DEPO-PROVERA is contraindicated in women who are pregnant.

Some reports suggest under certain circumstances, an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA injectable suspension 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 pregnancies while on DEPO-PROVERA are uncommon. There is no definitive information for the other formulations of DEPO-PROVERA, (**see Section 5.2 Pharmacokinetic properties - *Intramuscular formulations:*** Distribution).

If the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Lactation

DEPO-PROVERA and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child, (**see Section 5.2, Pharmacokinetic properties, *Intramuscular formulations:*** Distribution).

4.7 Effects on ability to drive and use machines

The effect of medroxyprogesterone acetate on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Contraception – Intramuscular (IM) Formulation [Appendix A, Appendix B]:

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, angioedema, drug hypersensitivity
Endocrine disorders	Prolonged anovulation
Psychiatric disorders	Depression, insomnia, nervousness, anorgasmia, libido decreased
Nervous system disorders	Seizure, dizziness, headache, somnolence
Vascular disorders	Embolism and thrombosis, hot flush
Gastrointestinal disorders	Abdominal pain, abdominal discomfort, nausea, abdominal distension
Hepatobiliary disorders	Jaundice, liver disorder
Skin and subcutaneous tissue disorders	Alopecia, acne, hirsutism, urticaria, lipodystrophy acquired*, pruritus, rash

Musculoskeletal and connective tissue disorders	Arthralgia, back pain, muscle spasms
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, pelvic pain, vaginitis, amenorrhoea, breast pain, vaginal discharge, breast tenderness
General disorders and administration site conditions	Fluid retention, pyrexia, fatigue, asthenia, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*
Investigations	Bone density decreased, glucose tolerance decreased, weight increased, weight decreased
*ADR identified post-marketing	

Additional Adverse Events Reported During Post-Marketing Experience:
Intramuscular Formulations:
In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA IM.

Gynecology – Intramuscular (IM) Formulation

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, angioedema, drug hypersensitivity
Endocrine disorders	Prolonged anovulation
Psychiatric disorders	Depression, insomnia, nervousness
Nervous system disorders	Dizziness, headache, somnolence
Vascular disorders	Embolism and thrombosis
Gastrointestinal disorders	Nausea
Hepatobiliary disorders	Jaundice, jaundice cholestatic
Skin and subcutaneous tissue disorders	Alopecia, hirsutism, acne, lipodystrophy acquired*, urticaria, pruritus, rash
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, uterine cervical erosion, breast pain, breast tenderness
General disorders and administration site conditions	Oedema, fluid retention, pyrexia, fatigue, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*
Investigations	Glucose tolerance decreased, weight increased, weight decreased
* ADR identified post-marketing	

Oncology [Appendix A, Appendix B]

System Organ Class	Adverse Drug Reactions
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, angioedema, drug hypersensitivity
Endocrine disorders	Corticoid-like effects, prolonged anovulation
Metabolism and nutritional disorders	Diabetes mellitus exacerbated, hypercalcaemia, weight fluctuation, increased appetite

Psychiatric disorders	Depression, confusion, nervousness, insomnia, euphoria, changes in libido
Nervous system disorders	Cerebral infarction, headache, dizziness, loss of concentration, somnolence, adrenergic-like effects, tremors
Eye disorders	Retinal embolism and thrombosis, cataract diabetic, visual impairment
Cardiac disorders	Cardiac failure congestive, myocardial infarction, tachycardia, palpitations
Vascular disorders	Embolism and thrombosis, thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Gastrointestinal disorders	Vomiting, diarrhoea, constipation, nausea, dry mouth
Hepatobiliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Alopecia, acne, hirsutism, lipodystrophy acquired*, urticaria, pruritus, rash, hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle spasms
Renal and urinary system disorders	Glycosuria
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), amenorrhoea, uterine cervical erosions, cervical discharge, galactorrhoea, breast pain, erectile dysfunction
General disorders and administration site conditions	Oedema/fluid retention, malaise, pyrexia, fatigue, injection-site reaction*, injection site persistent atrophy/indentation/dimpling*, injection site nodule/lump*, injection site pain/tenderness*
Investigations	Glucose tolerance decreased, blood pressure increased, liver function test abnormal, white blood cell count increased, platelet count increased
* ADR identified post-marketing	

Appendix A: ADRs and numeric frequencies listed in order of decreasing frequency within each SOC.

CONTRACEPTION (IM): ADRs and numeric frequencies listed in order of decreasing frequency within each SOC:

System Organ Class	ADR term (MedDRA 18.0 (when applicable))	Frequency n/N (%)
Immune system disorders	Drug hypersensitivity	0.36
	Anaphylactoid reaction	0.07
	Anaphylactic reaction	0.07
	Angioedema	0.07
Endocrine disorders	Prolonged anovulation	0.07
Psychiatric disorders	Nervousness	10.83
	Libido decreased	5.45
	Depression	1.48
	Insomnia	0.90
	Anorgasmia	0.07
Nervous system disorders	Headache	16.45
	Dizziness	5.62

System Organ Class	ADR term (MedDRA 18.0 (when applicable))	Frequency n/N (%)
	Somnolence	0.48
	Seizure	0.12
Vascular disorders	Hot flush	0.95
	(HLGT) Embolism and thrombosis	0.09
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort	11.24
	Nausea	3.31
	Abdominal distention	2.31
Hepatobiliary disorders	Liver disorder	0.24
	Jaundice	0.07
Skin and subcutaneous tissue disorders	Acne	1.19
	Alopecia	1.12
	Rash	1.10
	Pruritus	0.52
	Hirsutism	0.24
	Urticaria	0.21
	Lipodystrophy acquired*	0.07
Musculoskeletal and connective tissue disorders	Back pain	2.21
	Muscle spasms	0.07
	Arthralgia	0.07
Reproductive system and breast disorders	Vaginal discharge	2.93
	Breast tenderness	2.76
	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	0.57
	Galactorrhoea	0.52
	Pelvic pain	0.14
	Breast pain	0.07
	Amenorrhoea	0.07
	Vaginitis	0.07
General disorders and administration site conditions	Asthenia	4.24
	Fluid retention	2.17
	Fatigue	0.07
	Injection site reaction*	0.07
	Injection site persistent atrophy/indentation/dimpling*	0.07
	Injection site nodule/lump*	0.07
	Injection site pain/tenderness*	0.05
	Pyrexia	0.05
Investigations	Weight increased	69
	Weight decreased	25
	Bone density decreased	0.07
	Glucose tolerance decreased	0.07
*ADR identified post-marketing		

GYNECOLOGY (All Formulations Except For SC Formulation) - ADRs and numeric frequencies listed in order of decreasing frequency within each SOC:

System Organ Class	ADR PT in MedDRA Version 18.0 (when applicable)	Frequency n/N (%)
Immune system disorders	Drug hypersensitivity	2.35
	Anaphylactic reaction†	-
	Anaphylactoid reaction†	-
	Angioedema†	-
Endocrine disorders	Prolonged anovulation†	-
Psychiatric disorders	Depression	3.02
	Insomnia	1.68
	Nervousness	1.68
Nervous system disorders	Headache	12.08
	Dizziness	2.35
	Somnolence†	-
Vascular disorders	(HLGT) Embolism and thrombosis†	-
Gastrointestinal disorders	Nausea	10.40
Hepatobiliary disorders	Jaundice†, Jaundice cholestatic†	
Skin and subcutaneous tissue disorders	Acne	4.70
	Urticaria	2.01
	Pruritus	2.01
	Alopecia	1.01
	Hirsutism	0.34
	Lipodystrophy acquired*†	-
	Rash†	-
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	17.79
	Breast pain	3.69
	Breast tenderness	2.35
	Cervical discharge	1.01
	Galactorrhoea	0.67
	Amenorrhoea†	-
	Uterine cervical erosion†	-
General disorders and administration site conditions	Fatigue	3.69
	Injection site reaction	2.68
	Injection site persistent atrophy/indentation/dimpling*	1.37
	Pyrexia	1.34
	Injection site nodule/lump*	0.69
	Oedema, fluid retention	0.67
	Injection site pain/tenderness*	0.34
Investigations	Weight increased	2.01
	Weight decreased†	-
	Glucose tolerance decreased†	-
*ADR identified post-marketing † ADR not reported in the dataset		

ONCOLOGY- ADRs and numeric frequencies listed in order of decreasing frequency within each SOC:

System Organ Class	ADR term in MedDRA 17.0 *(when applicable)*	Incidence n/N (%)
Immune system disorders	Angioedema	0.22
	Drug hypersensitivity	0.07
	Anaphylactic reaction†	-
	Anaphylactoid reaction†	-
Endocrine disorders	Corticoid-like effects	0.97
	Prolonged anovulation†	-
Metabolism and nutritional disorders	Weight fluctuation	2.46
	Increased appetite	1.19
	Hypercalcaemia	0.22
	Diabetes mellitus exacerbated	0.15
Psychiatric disorders	Insomnia	1.65
	Euphoria	0.37
	Depression	0.22
	Changes in libido	0.15
	Nervousness	0.07
	Confusion†	-
Nervous system disorders	Tremors	1.8
	Headache	1.35
	Dizziness	1.2
	Somnolence	0.07
	Cerebral infarction	0.07
	Loss of concentration†	-
	Adrenergic-like effects†	-
Eye disorders	Visual iDepo-Proverairment†	-
	Cataract diabetic†	-
	Retinal embolism and thrombosis †	-
Cardiac disorders	Cardiac failure congestive	0.45
	Myocardial infarction	0.07
	Palpitations†	-
	Tachycardia†	-
Vascular disorders	Thrombophlebitis	0.6
	Embolism and thrombosis	0.07
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	0.15
Gastrointestinal disorders	Nausea	1.94
	Constipation	1.35
	Vomiting	1.12
	Diarrhoea	0.52
	Dry mouth	0.15
Hepatobiliary disorders	Jaundice	0.07
Skin and subcutaneous tissue disorders	Hyperhidrosis	2.31
	Hirsutism	0.45
	Acne	0.15
	Alopecia	0.07
	Rash	0.07
	Pruritus†	-
	Urticaria†	-

System Organ Class	ADR term in MedDRA 17.0 *(when applicable)*	Incidence n/N (%)
	Lipodystrophy acquired*†	-
Renal and urinary system disorders	Glycosuria†	-
Reproductive system and breast disorders	Erectile dysfunction	1.51
	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	0.69
	Breast pain	0.15
	Amenorrhoea†	-
	Uterine cervical erosions†	-
	Galactorrhoea†	-
	Cervical discharge†	-
General disorders and administration site conditions	Fatigue	4.18
	Injection-site reaction	3.4
	Oedema/fluid retention	1.72
	Injection site pain/tenderness*	0.08%
	Injection site persistent atrophy/indentation/dimpling*†	-
	Injection site nodule/lump*†	-
	Malaise	0.07
	Pyrexia	0.07
Musculoskeletal and connective tissue disorders	Muscle spasms	0.45
Investigations	Glucose tolerance decreased	0.07
	Blood pressure increased	0.07
	Liver function test abnormal†	-
	White blood cell count increased†	-
	Platelet count increased†	-
*ADR identified post-marketing † ADR not reported in the dataset		

Appendix B: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

CONTRACEPTION (IM):
The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 4200 women who received DEPO-PROVERA for contraception for up to 7 years. Those most frequently (>5%) reported adverse drug reactions were weight increased (69%), weight decreased (25%), headache (16%), nervousness (11%), abdominal pain or discomfort (11%), dizziness (6%), and decrease in libido (6%).

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
Immune system disorders			Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation
Psychiatric disorders	Nervousness	Depression, Libido decreased	Insomnia	Anorgasmia
Nervous system disorders	Headache	Dizziness	Seizure, Somnolence	
Vascular disorders			Hot flush	Embolism and thrombosis
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort,	Nausea, Abdominal distension		
Hepatobiliary disorders			Liver disorder	Jaundice
Skin and subcutaneous tissue disorders		Alopecia, Acne, Rash	Hirsutism, Urticaria, Pruritus	Lipodystrophy acquired*
Musculoskeletal and connective tissue disorders		Back pain		Arthralgia, Muscle spasms
Reproductive system and breast disorders		Vaginal discharge, Breast tenderness	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Galactorrhoea, Pelvic pain	Vaginitis, Amenorrhoea, Breast pain

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
General disorders and administration site conditions		Fluid retention, Asthenia		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation/dimpling*, Injection site nodule/lump*, Injection site pain/tenderness*
Investigations	Weight increased, Weight decreased			Bone density decreased, Glucose tolerance decreased
*ADR identified post-marketing				

GYNECOLOGY (All Formulations Except For SC Formulation):
The table below provides a listing of adverse drug reactions with frequency based on all-causality data from Phase 3 clinical studies that evaluated efficacy and safety of DEPO-PROVERA in gynecology. Those most frequently (>5%) reported adverse drug reactions were dysfunctional uterine bleeding (19%), headache (12%) and nausea (10%)**:**

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Not known (cannot be estimated from available data)
Immune system disorders		Drug hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders				Prolonged anovulation
Psychiatric disorders		Depression, Insomnia, Nervousness		
Nervous system disorders	Headache	Dizziness		Somnolence
Vascular disorders				Embolism and thrombosis
Gastrointestinal disorders	Nausea			
Hepatobiliary disorders				Jaundice, Jaundice cholestatic
Skin and subcutaneous tissue disorders		Alopecia, Acne, Urticaria, Pruritus,	Hirsutism	Lipodystrophy acquired*, Rash
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	Cervical discharge, Breast pain, Breast tenderness	Galactorrhoea	Amenorrhoea, Uterine cervical erosion
General disorders and administration site conditions		Pyrexia, Fatigue, Injection site reaction*, Injection site persistent atrophy/indentation /dimpling*	Oedema, Fluid retention, Injection site nodule/lump*, Injection site pain/tenderness*	
Investigations		Weight increased		Glucose tolerance decreased, Weight decreased
*ADR identified post-marketing				

ONCOLOGY:
The table below provides a listing of adverse drug reactions with frequency based on all-causality data from 1337 patients who received DEPO-PROVERA in 4 pivotal studies that evaluated efficacy and safety of DEPO-PROVERA for oncology indications.

System Organ Class	Very Common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Frequency Not Known (cannot be estimated from the available data)
Immune system disorders			Angioedema	Drug hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders			Corticoid-like effects		Prolonged anovulation
Metabolism and nutritional disorders		Weight fluctuation, Increased appetite	Diabetes mellitus exacerbated, Hypercalcaemia		
Psychiatric disorders		Insomnia	Depression, Euphoria, Changes in libido	Nervousness	Confusion
Nervous system disorders		Headache, Dizziness, Tremors		Cerebral infarction, Somnolence	Loss of concentration, Adrenergic-like effects
Eye disorders					Retinal embolism and thrombosis, Cataract diabetic, Visual iDepo-Proverairment
Cardiac disorders			Cardiac failure congestive	Myocardial infarction	Tachycardia, Palpitations
Vascular disorders			Thrombophlebitis	Embolism and thrombosis	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism		
Gastrointestinal disorders		Vomiting, Constipation, Nausea	Diarrhoea, Dry mouth		
Hepatobiliary disorders				Jaundice	

System Organ Class	Very Common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Frequency Not Known (cannot be estimated from the available data)
Skin and subcutaneous tissue disorders		Hyperhidrosis	Acne, Hirsutism	Alopecia, Rash	Lipodystrophy acquired*, Urticaria, Pruritus
Musculoskeletal and connective tissue disorders			Muscle spasms		
Renal and urinary system disorders					Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain		Amenorrhoea, Uterine cervical erosions, Cervical discharge, Galactorrhoea
General disorders and administration site conditions		Oedema /fluid retention, Fatigue, Injection site reaction*	Injection site pain/tenderness*	Malaise, Pyrexia	Injection site persistent atrophy/indentation/dimpling*, Injection site nodule/lump*
Investigations				Glucose tolerance decreased, Blood pressure increased	Liver function test abnormal, White blood cell count increased, Platelet count increased
*ADR identified post-marketing					

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

To report side effects:

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)
- SFDA Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

Overdose treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medroxyprogesterone acetate (17a-hydroxy-6a-methylprogesterone acetate) is a derivative of progesterone.

Mechanism of Action
DEPO-PROVERA is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been demonstrated to possess several pharmacologic actions on the endocrine system:

- Inhibition of pituitary gonadotropins (FSH and LH);
- Decrease of ACTH and hydrocortisone blood levels;
- Decrease of circulating testosterone;
- Decrease of circulating estrogen levels (as the result of both FSH inhibition and enzymatic induction of hepatic reductase, resulting in increased clearance of testosterone and consequent decreased conversion of androgens to estrogens).

All of these actions result in a number of pharmacological effects, as described below.

Contraception
DEPO-PROVERA, when administered parenterally at the recommended dose to women, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus.

Gynecology
Medroxyprogesterone acetate (DEPO-PROVERA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered DEPO-PROVERA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Endometriosis
Suppression of serum estradiol concentrations and a possible direct action of DMPA SC on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Oncology
DEPO-PROVERA demonstrates antitumor activity. When DEPO-PROVERA is given to patients at high doses (either by the oral route or by IM injection) it is effective in the palliative treatment of hormone-responsive malignant neoplasms.

Clinical Studies
<u>BMD Studies</u>

BMD Changes in Adult Women

In a non-randomized controlled clinical study comparing adult women using DEPO-PROVERA contraceptive injection (150 mg IM) for up to 5 years to women who elected to use no hormonal contraception, 42 DEPO-PROVERA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DEPO-PROVERA. Among DEPO-PROVERA users, BMD declined during the first 2 years of use, with little 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. There were no significant changes in BMD in the control women over the same period of time.

BMD recovery post-treatment in adult women

In the same study population, there was partial recovery of BMD toward baseline values during the 2-year period after stopping use of DEPO-PROVERA injection (150 mg IM)

After 5 years of treatment with DEPO-PROVERA injection (150 mg IM), the mean % change in BMD from baseline was -5.4%, -5.2% and -6.1% at the spine, total hip and femoral neck, respectively, while untreated control women, over the same time interval, showed mean changes from baseline of +/- 0.5% or less at the same skeletal sites. Two years after stopping DEPO-PROVERA injections, mean BMD had increased at all 3 skeletal sites but deficits remained: -3.1%, -1.3% and -5.4% at the spine, total hip and femoral neck, respectively. At the same time point, women in the control group showed mean changes from baseline BMD of 0.5%, 0.9% and -0.1% at the spine, total hip and femoral neck, respectively.

BMD Changes in Adolescent Females (12-18 years)

The effect of DEPO-PROVERA injectable (150 mg IM) use on BMD for up to 240 weeks (4.6 years) was evaluated in an open-label non-comparative clinical study of 159 adolescent females (12-18 years) who elected to begin treatment with DEPO-PROVERA; 114 of the 159 participants used DEPO-PROVERA continuously (4 injections during each 60-week period) and had BMD measured at Week 60. BMD declined during the first 2 years of use with little change in subsequent years. After 60 weeks of DEPO-PROVERA use, mean % BMD changes from baseline were -2.5%, -2.8% and -3.0% at the spine, total hip and femoral neck, respectively. A total of 73 subjects continued to use DEPO-PROVERA through 120 weeks; mean % BMD changes from baseline were -2.7%, -5.4% and -5.3% at the spine, total hip and femoral neck, respectively. A total of 28 subjects continued to use DEPO-PROVERA through 240 weeks; mean % BMD changes from baseline were -2.1%, -6.4% and -5.4% at the spine, total hip and femoral neck, respectively.

BMD recovery post-treatment in adolescents
In the same study, 98 adolescent participants received at least 1 DEPO-PROVERA injection and provided at least 1 follow-up BMD measurement after stopping DEPO-PROVERA use, with DEPO-PROVERA treatment for up to 240 weeks (equivalent to 20 DEPO-PROVERA injections) and post-treatment follow-up extending for up to 240 weeks after the final DEPO-PROVERA injection**.** The median number of injections received during the treatment phase was 9. At the time of the final DEPO-PROVERA injection, BMD % changes from baseline were -2.7%, -4.1% and -3.9% at the spine, total hip and femoral neck, respectively. Over time these mean BMD deficits fully recovered after DEPO-PROVERA was discontinued. Full recovery required 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck. Longer duration of treatment and smoking were associated with slower recovery. See **Section 4.4. Special warnings and precautions for use - *Additional Warnings and Precautions for Specific Use or Formulation,*** Contraception/Endometriosis - Injectable Formulations: Loss of Bone Mineral Density (BMD).

Relationship of fracture incidence to use of DEPO-PROVERA injectable (150 mg IM) or non-use by women of reproductive age
A retrospective cohort study to assess the association between DEPO-PROVERA injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence

rates of fracture were compared before and after DEPO-PROVERA use started and also between DEPO-PROVERA users and women who used other contraceptives but had no recorded use of DEPO-PROVERA. Among women using DEPO-PROVERA, use of DEPO-PROVERA was not associated with an increase in fracture risk (incident rate ratio = 1.01, 95% CI 0.92-1.11, comparing the study follow-up period with up to 2 years of observation prior to DEPO-PROVERA use). However, DEPO-PROVERA users did have more fractures than non-users not only after first contraceptive use (IRR = 1.23, 95% CI 1.16-1.30), but also before first contraceptive use (IRR = 1.28, 95% CI 1.07-1.53).

In addition, fractures at the specific bone sites characteristic of osteoporotic fragility fractures (spine, hip, pelvis) were not more frequent among DEPO-PROVERA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23), nor was there any evidence that longer use of DEPO-PROVERA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

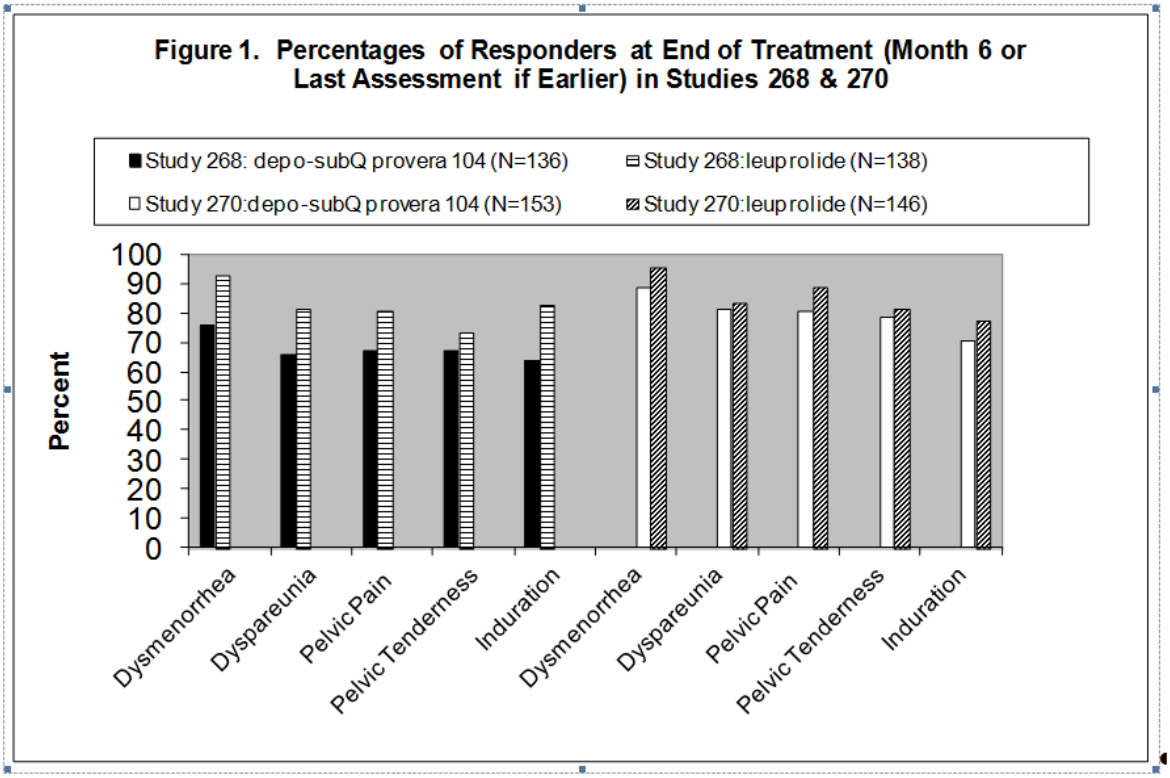
These data demonstrate that DEPO-PROVERA users have an inherently different fracture risk profile to non-users for reasons not related to DEPO-PROVERA use.

Maximum follow-up in this study was 15 years, therefore, possible effects of DEPO-PROVERA that might extend beyond 15 years of follow-up cannot be determined.

Endometriosis Studies

The efficacy of DEPO-PROVERA SC in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in two active comparator -controlled studies. Each study assessed reduction in endometriosis-associated pain over 6 months of treatment and recurrence of symptoms for 12 months post treatment. Subjects treated with DEPO-PROVERA SC for 6 months received a 104 mg dose every 3 months (2 injections), while women treated with leuprolide microspheres for 6 months received a dose of 11.25 mg every 3 months (2 injections) or 3.75 mg every month (6 injections). Study 268 was conducted in the USA and Canada and enrolled 274 subjects (136 on DEPO-PROVERA SC and 138 on leuprolide). Study 270 was conducted in South America, Europe and Asia, and enrolled 299 subjects (153 on DEPO-PROVERA SC and 146 on leuprolide).

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



Favorable Response = reduction in severity of symptom or sign of ≥1 point on a scale of 0 to 3, as compared to baseline.

Additionally, scores from each of the five categories were combined, with the total (composite score) considered a global measurement of overall disease improvement. For subjects with baseline scores for each of the 5 categories, a mean decrease of 4 points relative to baseline was considered a clinically meaningful improvement. Across both studies, for both treatment groups, the mean changes in the composite score met the protocol-defined criterion for improvement.

In the clinical trials, treatment with DEPO-PROVERA SC was limited to six months. Data on the persistence of benefit with longer treatment are not available.

Subjects recorded daily the occurrence and severity of hot flushes. Of the DEPO-PROVERA SC users, 28.6% reported experiencing moderate or severe hot flushes at baseline, 36.2% at Month 3, and 26.7% at Month 6. Of the leuprolide users, 32.8% reported experiencing moderate or severe hot flushes at baseline, 74.2% at Month 3, and 68.5% at Month 6.

Women's Health Initiative Study

The WHI CEE (0.625mg)/DEPO-PROVERA (2.5mg) trial enrolled 16,608 postmenopausal women aged 50-79 years with intact uteri at baseline, to assess the risks and benefits of the combined therapy compared with placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. The study was stopped early after an average follow-up of 5.2 years (planned duration 8.5 years) because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index" (**see Section 4.4. Special warnings and precautions for use**, Breast Cancer).

The combination CEE/DEPO-PROVERA therapy reported a significant decrease in osteoporotic (23%) and total (24%) fractures.

Million Women Study
The MWS was a prospective cohort study enrolling 1,084,110 women in the UK aged 50-64 years of whom 828,923 with defined time since menopause were included in the main analyses of risk of breast cancer in relation to HT. Overall, 50% of the study population had used HT at some point. Most current users of HT at baseline reported using preparations containing estrogen only (41%) or estrogen-progestin combinations (50%). The average duration of follow-up was 2.6 years for analyses of cancer incidence and 4.1 years for analyses of mortality (**see Section 4.4 Special warnings and precautions for use,** Breast Cancer).

Heart and Estrogen/progestin Replacement Studies
HERS and HERS II studies were two randomized, prospective secondary prevention trials on the long-term effects of oral continuous combined CEE/DEPO-PROVERA (0.625 mg CEE plus 2.5mg DEPO-PROVERA) regimen in postmenopausal women with CHD (**see Section 4.4. Special warnings and precautions for use -** Cardiovascular disorders). 2, 763 postmenopausal women with a mean age of 66.7 years and with intact uteri were enrolled in this study. The average duration of follow-up was 4.1 years for HERS and 2.7 additional years (for a total of 6.8 years) for HERS II (**see Section 4.4. Special warnings and precautions for use -** Cardiovascular Disorders).

Women's Health Initiative Memory Study
The WHIMS, a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women age 65 to 79 years to evaluate the effects of CEE/DEPO-PROVERA (0.625 mg CEE plus 2.5 mg DEPO-PROVERA) or CEE-alone (0.625 mg) on the incidence of probable dementia compared with placebo. The average duration of follow-up was 4.05 years for the CEE/DEPO-PROVERA (**see Section 4.4. Special warnings and precautions for use -** Dementia).

5.2 Pharmacokinetic properties

Subcutaneous formulation

Absorption
MPA absorption from the SC injection site to achieve therapeutic levels is relatively prompt. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.
Effect of Injection Site
DMPA subcutaneous was administered into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations ($C_{min;}$ Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution
Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin; no binding of MPA occurs with Sex Hormone-Binding Globulin (SHBG).

Metabolism
MPA is extensively metabolized in the liver.

Elimination
Residual MPA concentrations at the end of the dosing interval (3 months) of DMPA sucutaneous are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Special Populations:

Race
There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of DMPA subcutaneous among women of all ethnic backgrounds studied. The pharmacokinetics/dynamics of DMPA has been evaluated in Asian women in a separate study.

Effect of Body Weight
No dosage adjustment of DMPA subcutaneous is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n = 42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m^2). The AUC_{0-91} values for MPA were 68.5, 74.8, and 61.8 ng day/mL in women with BMI categories of ≤25 kg/m^2, >25 kg/m^2 to ≤30 kg/m^2, and >30 kg/m^2, respectively. The mean MPA Cmax was 1.65 ng/mL in women with BMI ≤25 kg/m^2, 1.76 ng/mL in women with BMI >25 kg/m^2 to ≤30 kg/m^2, and 1.40 ng/mL in women with BMI >30 kg/m^2, respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Intramuscular formulations

Absorption
Following intramuscular administration, DEPO-PROVERA is slowly released, resulting in low, but persistent levels in the circulation. Immediately after intramuscular injection of 150mg/ml DEPO-PROVERA, plasma levels were 1.7 ± 0.3 nmol/L. Two weeks later, levels were 6.8 ± 0.8 nmol/L. Mean time to peak is approximately 4 to 20 days following an intramuscular dose. Serum medroxyprogesterone acetate levels gradually decline and remain relatively constant at about 1 ng/mL for 2-3 months. Circulating levels can be detected for as long as 7 to 9 months following an intramuscular injection.

Distribution
DEPO-PROVERA is approximately 90 to 95 % protein bound. Volume of distribution is reported as 20 ± 3 liters. Medroxyprogesterone acetate crosses the blood-brain-barrier, and the placental barrier (**see Section 4.6. Pregnancy and lactation**). Low levels of medroxyprogesterone acetate have been detected in breast milk of lactating women (**see Section 4.6 – Pregnancy and lactation**) administered 150 mg of medroxyprogesterone acetate by the IM route.

Metabolism
DEPO-PROVERA is metabolized in the liver.

Elimination
The elimination half-life following single intramuscular injection is about 6 weeks. Medroxyprogesterone acetate is primarily excreted in the feces, via biliary secretion. Approximately 30% of an intramuscular dose is secreted in the urine after 4 days.

Oral formulations

Absorption
Oral medroxyprogesterone (MPA) is rapidly absorbed with maximum concentration obtained between 2 to 4 hours. The half-life of oral MPA is approximately 17 hours. It is 90% protein bound, and is mainly excreted in the urine.
Administration with food increases the bioavailability of MPA. A 10 mg dose of oral MPA, taken immediately before or after a meal, increased average MPA C_{max} (51 and 77%, respectively) and average AUC (18 and 33%, respectively). The half-life of MPA was not changed with food.

Distribution
MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex hormone-binding globulin. The unbound MPA modulates pharmacologic responses.

Metabolism
Following oral dosing, MPA is extensively metabolized in the liver via ring A and/or side-chain hydroxylation, with subsequent conjugation and elimination in the urine. At least 16 MPA metabolites have been identified. In a study designed to measure the metabolism of medroxyprogesterone acetate (MPA), the results suggest that human cytochrome P450 3A4 is primarily involved in the overall metabolism of MPA in human liver microsomes.

Elimination
Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact MPA after a 10 mg or 100 mg dose was 7.3% and 6.4%, respectively. Elimination half-life of oral MPA is 12 to 17 hours.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term intramuscular administration of medroxyprogesterone acetate (DEPO-PROVERA) has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of oral DEPO-PROVERA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350, polysorbate 80, sodium chloride, methyl parahydroxybenzoate, propyl parahydroxybenzoate, water for injections, hydrochloric acid and/or sodium hydroxide for the pH adjustment.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 Months.

Do not use DEPO-PROVERA after the expiry date which is stated on the carton / Vial label after EXP:. The expiry date refers to the last day of that month.
The expiry date is mentioned on the package after the letters EXP. (EXP. = expiry date).

6.4 Special precautions for storage

Store below 30°C
Do not refrigerate or freeze.
Store vial upright.

6.5 Nature and contents of container

Sterile aqueous suspension for intramuscular injection.

Presentations:
DEPO-PROVERA 150 mg suspension for injection:
- 3.3 ml vial

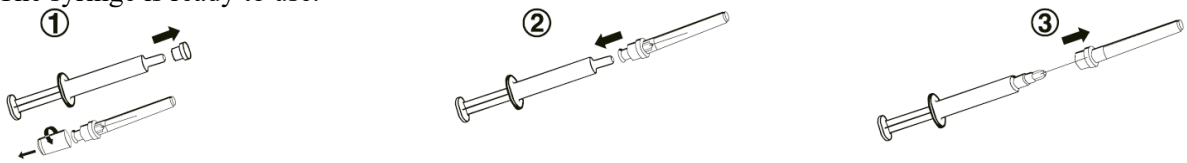
6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Vial: shake well just before use in order to obtain homogeneous suspension.

Pre-filled syringe: shake well just before use in order to obtain homogeneous suspension.
1. Remove the protective cap.
2. Fit the needle to the syringe.
3. Remove the protective sheath from the needle.

The syringe is ready to use.



After use, the syringe cannot be reused and must be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION:

MARKETING AUTHORISATION HOLDER:
Pfizer S.A., 17 Boulevard de la Plaine, 1050 Brussels, Belgium.

Manufactured By:
Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870Puurs-Sint-Amands, Belgium.

8. DATE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 01-Jan-1989

9. DATE OF REVISION OF THE TEXT:

December 2023