Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Provera 2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg medroxyprogesterone acetate

Excipients with known effect:
Lactose monohydrate 84.0 mg, sucrose 1.375 mg, sunset yellow (E110) 0.019 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Orange, round, convex tablets scored on one side and marked "U64" on the other one.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen. Indicated for dysfunctional (anovulatory) uterine bleeding where progesterone deficiency exists, secondary amenorrhoea, and mild to moderate endometriosis. Also indicated for use in the menopause to oppose the endometrial effects of oestrogen in post-menopausal women being treated with oestrogen.

4.2 Posology and method of administration

Posology

Use of combined oestrogen/progestin therapy in post-menopausal women should be limited to the lowest effective dose and the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated (see section 4.4).

Adults:
Dysfunctional (anovulatory) uterine bleeding: 2.5 - 10 mg daily for 5 - 10 days commencing on the assumed or calculated 16th - 21st day of the cycle. Treatment should be given for two consecutive cycles. When bleeding occurs from a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with medroxyprogesterone acetate (MPA) in doses of 5 - 10 mg for 10 days.

Secondary amenorrhoea: 2.5 to 10 mg daily for 5 to 10 days commencing on the assumed or calculated 16th - 21st day of the cycle. Treatment should be given for three consecutive cycles. In amenorrhoea associated with a poorly developed proliferative endometrium, conventional oestrogen therapy may be used in conjunction with medroxyprogesterone acetate, the latter in doses of 5-10 mg for 10 days.

Mild to moderate endometriosis: Beginning on the first day of the menstrual cycle, 10 mg three times a day for 90 consecutive days.

As an adjunct to oestrogens in post-menopausal women undergoing treatment with oestrogens: 10 mg per day for 10 - 12 days beginning on the 16th day of a 28 day course of oestrogen therapy. Withdrawal progestin bleeding should occur, beginning on the 3rd to 7th day after Provera treatment.

Elderly: Not applicable.

*Paediatric population:*Not applicable.

Method of administration

For oral use

4.3 Contraindications

Known, past or suspected breast cancer

Use in patients with genital cancer

Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal.

Use in patients with a history of or existing thromboembolic disorders or thromboembolism.

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)

Use in patients with undiagnosed, irregular vaginal bleeding

Use in pregnancy or suspected pregnancy (see section 4.6).

Use in patients with undiagnosed breast pathology.

Hypersensitivity to active substance or to any of the excipients listed in section 6.1.

Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical Examination/Follow-Up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need Supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Provera, in particular:

–Leiomyoma (uterine fibroids) or endometriosis

–A history of, or risk factors for, thromboembolic disorders (see below)
–Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
–Hypertension
–Liver disorders (e.g. liver adenoma)
–Diabetes mellitus with or without vascular involvement
–Cholelithiasis
–Migraine or (severe) headache
–Systemic lupus erythematosus.
–A history of endometrial hyperplasia (see below)
–Epilepsy
–Asthma
–Otosclerosis

Reasons for Immediate Withdrawal of Therapy:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

–Jaundice or deterioration in liver function
–Significant increase in blood pressure
–New onset of migraine-type headache
–Pregnancy

Endometrial Hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast Cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous Thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for

users compared with non-users.

For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary Artery Disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian Cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRTs confers a different risk than oestrogen-only products.

Fluid Retention

MPA 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.

Dementia

Pooling data from the Women's Health Initiative Memory Study (WHIMS) (see section 5.1, Clinical Studies), a substudy of WHI, for CEE-alone and CEE/MPA reported an increased risk of developing probable dementia and mild cognitive impairment (MCI) in postmenopausal women 65 years of age or older. Use of HRT to prevent dementia or MCI in women is not recommended.

Unexpected vaginal bleeding during therapy with Provera should be investigated. (See section 4.3).

A negative pregnancy test should be demonstrated immediately before starting therapy with Provera.

Depression may occur with treatment. Provera should be used with caution in patients with a history of or existent depression, patients should be carefully monitored.

Provera, especially in the high doses used for cancer therapy, may cause weight gain and fluid retention. These patients should be kept under special surveillance. With this in mind, caution should be exercised in treating any patient with a pre-existing medical condition, such as epilepsy, migraine, asthma, hypertension, cardiac or renal dysfunction that might be adversely affected by weight gain or fluid retention. These patients should be kept under special surveillance. Regular monitoring of blood pressure should be carried out in hypertensive patients.

Some patients receiving low dose Provera may exhibit a decreased glucose tolerance. Patients with diabetes should be carefully supervised.

If endometrial or endocervical tissue is submitted for examination, the pathologist (laboratory) should be informed of the patient's use of Provera.

The physician/laboratory should be informed that the use of Provera may decrease levels of the following endocrine biomarkers.

a) plasma/urinary steroids (eg cortisol, oestrogen, pregnanediol, progesterone, testosterone)
b) plasma/urinary gonadotrephins (eg LH and FSH)
c) Sex-hormone-binding-globulin.

Medication should not be re-administered 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 re-administered.

Studies in animals have indicated that administration of very high doses of oestrogens and/or progestogens will induce neoplastic mammary tumours in some animal species, in particular the dog. Investigations suggest that results of dosing studies with progestogen in the dog are irrelevant to the potential for such effects in human beings, because of the difference in mammary receptor susceptibility and response. No evidence has been found in human beings to suggest a relationship between administration of progesterone or progestogens alone and the development of neoplasia.

Theoretical evidence suggests that use of progesterones should be interrupted for an interval to permit return to normal hypothalamo-pituitary-gonadal function. While it is not yet possible to state even a provisionally acceptable interval, any prescriber should bear this matter in mind when organising prolonged use of such agents.

Provera has not been causally associated with the induction of thrombotic or thrombo-embolic disorders; however any patient with a history or who develops this kind of event while undergoing treatment with Provera should have their status and need for treatment assessed before continuing therapy.

Several randomised, prospective trials on the long-term effects of a combined oestrogen/progestin regimen in postmenopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g. coronary heart disease and stroke), breast cancer and venous thromboembolism.

These products should be discontinued before elective surgery or during enforced bed rest.

This product contains lactose, sucrose and E110.

- Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Sunset yellow colour (E110): This may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with high doses of Provera may significantly depress the bioavailability of Provera. Interactions with other medicinal treatments (including oral anti-coagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (Hypericum Perforatum) may induce the metabolism of oestrogens and progestogens. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy
Some reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in the male and female foetuses.

Progesterone and certain progestogens have been shown to produce reversible virilization in some female offspring of women treated with such substances during pregnancy. Pregnancy should be excluded before treatment is begun. Provera is contra-indicated in pregnant women (see section 4.3).

If Provera is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be appraised of the potential hazard to the foetus.

Lactation
The drug and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child.

4.7 Effects on ability to drive and use machines

No adverse effect has been reported.

4.8 Undesirable effects

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 DMPA in gynaecology. Those most frequently (>5%) reported adverse drug reactions were dysfunctional uterine bleeding (19%), headache (12%) and nausea (10%).

The following lists of adverse reactions are listed within the organ system classes, under headings of frequency (number of patients expected to experience the reaction), using the following categories:
Very common (≥1/10)

Common (≥1/100 to <1/10);
Uncommon (≥1/1000 to <1/100);
Rare (≥1/10,000 to <1/1000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

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	Very Rare < 1/10,000	Frequency 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			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	Oedema, Fluid retention			
Investigations		Weight increased				Glucose tolerance decreased, Weight decreased

Breast cancer
According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For oestrogen plus progestogen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWSreported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be

For users of oestrogen-only replacement therapy,

- between 0 and 3 (best estimate = 1.5) for 5 years' use
- between 3 and 7 (best estimate = 5) for 10 years' use.

For users of oestrogen plus progestogen combined HRT,

- between 5 and 7 (best estimate = 6) for 5 years' use
- between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestogen combined HRT (CEE + MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:

For 1000 women in the placebo group,

- about 16 cases of invasive breast cancer would be diagnosed in 5 years.

For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of additional cases would be

- between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).'

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens.

According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

–Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
–Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see sections 4.3 and 4.4.
–Myocardial infarction and stroke
–Gall bladder disease.
–Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
–Probable dementia (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

In animals Provera has been shown to be capable of exerting an adreno-corticoid effect, but this has not been reported in the human, following usual dosages. The oral administration of Provera at a rate of 100 mg per day has been shown to have no effect on adrenal function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens – Pregnen (4) derivatives, ATC code: G03DA02,

Medroxyprogesterone acetate (MPA) is a synthetic progestogen structurally related to progestogen, with actions and uses similar to those of the progestogens in general.

MPA has minimal androgenic activity compared to progesterone and virtually no oestrogenic activity.

Progestogens are used in the treatment of dysfunctional uterine bleeding, secondary amenorrhoea and endometriosis.

5.2 Pharmacokinetic properties

MPA is readily absorbed from the GI tract with a single oral dose of 10-250 mg. The time taken to reach the peak serum concentration (T_{max}) was 2-6 hours and the average peak serum concentration (C_{max}) was 13-46.89 mg/ml.

Unmetabolised MPA is highly plasma protein bound. MPA is hydroxylated in the liver.

MPA is primarily metabolised by faecal excretion as glucuronide conjugated metabolite.

Metabolised MPA is excreted more rapidly and in greater percentage following oral doses than after aqueous intramuscular injection.

MPA is reported to be excreted in breast milk.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Sucrose
Maize starch
Liquid paraffin
Talc
Calcium stearate
Sunset Yellow FCF (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottle pack: 5 years
Blister pack: 4 years

6.4 Special precautions for storage

Blister pack: Do not store above 25°C.

6.5 Nature and contents of container

HDPE tamper-evident bottles with LDPE push-fit tamper-evident caps, containing 100 tablets.

Aluminium foil/PVC blister strips of 10 tablets, each box containing 3 strips (30 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/134/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 1993
Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT