NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PROVERA® 2.5 mg, 5 mg, 10 mg, 100 mg and 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablet contains 2.5 mg, 5 mg, 10 mg, 100 mg and 200 mg of medroxyprogesterone acetate (MPA) as the active ingredient.

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water. MPA is 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate.

Excipient(s) with known effect

PROVERA 2.5 mg, 5 mg and 10 mg tablets:

- Lactose monohydrate,
- Sucrose.

PROVERA 100 mg and 200 mg tablets:

- Isopropyl alcohol,
- Sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PROVERA 2.5 mg tablets are orange, circular, scored one side, marked U64 on the other.

PROVERA 5 mg tablets are blue, circular, scored one side and marked 286 on both sides of the score line, marked U on the other.

PROVERA 10 mg tablets are white, circular, scored marked UPJOHN 50.

PROVERA 100 mg tablets are white, scored, marked U467.

PROVERA 200 mg tablets are white, scored, marked U320.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROVERA 2.5 mg, 5 mg and 10 mg tablets are indicated for**:**

- diagnosis of primary and secondary amenorrhoea
- treatment of dysfunctional (anovulatory) uterine bleeding
- opposition of endometrial effects of estrogen in menopausal women being treated with estrogen (hormone replacement therapy, now referred to as menopausal hormone therapy (MHT))
- treatment of endometriosis.

PROVERA 100 mg and 200 mg tablets are indicated as adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma and, in the treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women.

4.2 Dose and method of administration

Use of combined estrogen-progestogen therapy in postmenopausal 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).

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

Diagnosis of primary and secondary amenorrhoea

2.5 mg to 10 mg per day for 5 to 10 days.

Dysfunctional (anovulatory) uterine bleeding

2.5 mg to 10 mg per day for 5 to 10 days for 2 to 3 cycles and then discontinued to see if the dysfunction has regressed. If bleeding occurs from a poorly proliferative endometrium, estrogens should be used concomitantly with PROVERA therapy.

Opposition of endometrial effects of estrogen in menopausal women being treated with estrogen (MHT)

For women taking 0.625 mg of conjugated estrogen or an equivalent daily dose of another estrogen, PROVERA can be given in 1 or 2 regimens:

- Continuous regimen of 2.5 mg to 5.0 mg daily.
- Sequential regimen of 5 mg to 10 mg daily for 10 to 14 consecutive days of a 28-day or monthly cycle.

Endometriosis

10 mg 3-times a day for 90 consecutive days, beginning on the first day of the menstrual cycle.

Endometrial and renal carcinoma

100 mg to 600 mg per day is recommended.

Breast cancer

400 mg to 1500 mg per day is recommended. The patient should then be continued on therapy as long as she is responding to treatment.

NOTE: Response to hormonal therapy for endometrial, renal or breast cancer may not be evident until after 8 to 10 weeks of therapy. In the event of a rapid progression of disease at any time during therapy, treatment with PROVERA should be terminated.

PROVERA is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced, inoperable cases including those with recurrent or metastatic disease.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet (see section 6.1)
- known or suspected pregnancy (see sections 4.4 and 4.6)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Warnings

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma - for ≥100 mg dose tablets

Meningiomas have been reported following long-term administration of MPA (see Section 5.1). Patients treated with MPA should be monitored for signs and symptoms of meningiomas in accordance with clinical practice.

If a patient treated with MPA for a non-oncological indication is diagnosed with meningioma, MPA should be discontinued. Caution is advised when recommending MPA to patients with a history of meningioma.

If a patient treated with MPA for oncological indication is diagnosed with meningioma, the need for further treatment with MPA should be carefully considered on a case-by-case basis taking into account individual benefits and risks. Caution is advised when recommending MPA to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is 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 be withdrawn.

Adrenocorticoid function

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Effects of laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex-hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen-progestogen 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.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of MHT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination MHT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

A large meta-analysis of observational studies reported that when estrogen-plus-progestin therapy was taken for more than 5 years, the increased risk of breast cancer may persist for 10 years or more after discontinuation of treatment. The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years. In current users the increased risk of breast cancer in women taking combined estrogen-progestin for MHT becomes apparent after about 1-4 years.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-alone or combined estrogen-progestogen MHT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the Women's Health Initiative trial, suggest that the long-term use of combined MHTs may be associated with a similar or slightly smaller risk (see section 4.8).

The benefits and risks of MHT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen-progestogen therapy in postmenopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. MHT in postmenopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in bone mineral density

There are no studies on the bone mineral density (BMD) effects of PROVERA.

Use of Depo-Provera (DMPA) 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 DMPA injection during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass (see section 5.1, Clinical Efficacy and Safety, BMD changes in adult women and BMD changes in adolescent females).

In both adult women and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after DMPA injection is discontinued and ovarian estrogen production increases. In adults, BMD was observed for a period of 2 years after DMPA 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, Clinical Efficacy and Safety, BMD

recovery post-treatment in adult women). After discontinuing DMPA 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, Clinical Efficacy and Safety, BMD recovery post-treatment in adolescent females).

A large observational study of female contraceptive users showed that use of DMPA injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures (see section 5.1, Clinical Efficacy and Safety, Relationship of fracture incidence to use of DMPA injection (150 mg) or non-use by women of reproductive age).

An evaluation of BMD may be appropriate in some patients who use PROVERA long term.

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

Precautions

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

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

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a MHT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of MHT to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration of MPA with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration of MPA with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

The definition of Pregnancy Category D is drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. 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 may be approximately doubled with exposure to progesterones.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of MHT. An endometrial biopsy may be performed at the discretion of the attending physician.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of MPA 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 in women on MPA are uncommon. There is no definitive information for the other formulations of MPA.

Breast-feeding

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

Fertility

MPA given orally at 1, 10 and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

4.7 Effects on ability to drive and use machinery

No data available.

4.8 Undesirable effects

The following events are associated with the use of progestogens including MPA:

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Metabolism and nutrition disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, increased appetite.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Eye disorders: retinal embolism, cataract diabetic, visual impairment.

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

Hepatobiliary disorders: jaundice, jaundice cholestatic, disturbed liver function.

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), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, mastodynia.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see section 4.4, Warnings).

General disorders and administration site conditions: changes in appetite, oedema, fluid retention, pyrexia, malaise, fatigue.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels.

Ovarian cancer

Use of estrogen-only and or combined estrogen-progestogen MHT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4, Warnings, Ovarian cancer).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using MHT compared to women who have never used MHT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of MHT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking MHT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Post-marketing Experience

The following adverse events have been reported during post-marketing experience.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Similar to progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical Efficacy and Safety

BMD changes in adult women

There are no studies on the BMD effects of PROVERA.

In a non-randomised controlled clinical study comparing adult women using DMPA injection (150 mg every 3 months for contraception) to women who elected to use no hormonal contraception, 42 DMPA users completed 5 years of treatment and provided at least 1 follow-up BMD measurement after stopping DMPA. Among DMPA users, BMD declined during the first 2 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. 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 DMPA injection (150 mg).

After 5 years of treatment with DMPA injection (150 mg), 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 DMPA 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 DMPA injectable (150 mg) 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 DMPA; 114 of the 159 participants used DMPA 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 DMPA 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 DMPA 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 DMPA 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 adolescent females

In the same study, 98 adolescent participants received at least 1 DMPA injection and provided at least 1 follow-up BMD measurement after stopping DMPA use, with DMPA treatment for up to 240 weeks (equivalent to 20 DMPA injections) and post-treatment follow-up extending for up to 240 weeks after the final DMPA injection. The median number of injections received during the treatment phase was 9. At the time of the final DMPA 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 DMPA 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, Warnings, Decrease in bone mineral density).

Relationship of fracture incidence to use of DMPA injection (150 mg) or non-use by women of reproductive age

A retrospective cohort study to assess the association between DMPA injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users. The incidence rates of fracture were compared before and after DMPA use and also between DMPA users and women who used other contraceptives but had no recorded use of DMPA. Among DMPA users, DMPA was not associated with an increase in fracture risk (incident rate ratio (IRR) = 1.01, 95% CI 0.92-1.11, comparing the study follow-up period with up to 2 years of observation prior to DMPA use). However, DMPA users had more fractures than non-users after first contraceptive use (IRR = 1.23, 95% CI 1.16-1.30) and 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 DMPA users compared to non-users (IRR = 0.95, 95% CI 0.74-1.23). There was also no evidence that longer use of DMPA (2 years or more) confers greater risk for fracture compared to less than 2 years of use.

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

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

Observational studies of breast cancer risk

A large meta-analysis of observational studies generated evidence for the type and timing of MHT on breast cancer risk. After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use.

It was reported that, when estrogen-plus-progestin therapy was taken for more than 5 years, the increased risk may persist for 10 years or more after discontinuation of treatment:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	5-9 years	1.19 (1.10-1.28)
	≥10 years	≥10 years	1.28 (1.15-1.43)

The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen+progestin	≥10 years	<1 year	1.06 (0.95-1.19)
	≥10 years	1-4 years	1.09 (1.00-1.18)

In current users, the increased risk of breast cancer in women taking combined estrogen-progestin MHT becomes apparent after about 1-4 years:

MHT type	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	<1 year	1.08 (0.86-1.35)
	1-4 years	1.17 (1.10-1.26)
Estrogen+progestin	<1 year	1.20 (1.01-1.43)
	1-4 years	1.60 (1.52-1.69)

Meningioma - for ≥100 mg dose tablets

Based on results from a French epidemiological case-control study, an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French national health data system (SNDS – Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma and 90,305 women without meningioma. The exposure to medroxyprogesterone acetate 150 mg/3 mL injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 mL (9/18,061 (0.05%) v 11/90,305 (0.01%), OR 5.55 (95% CI 2.27–13.56)). This excess risk seems to be driven primarily by prolonged use of medroxyprogesterone acetate.

Based on results from a matched case–control study from the United States, medroxyprogesterone acetate use was associated with increased odds of the presence of meningioma with evidence of increased odds with increasing duration of use. Data were obtained from the IBM MarketScan claims database for the years 2006–2022. A total of 117,503 cases and 1,072,907 matched controls were included in the analysis. For all meningiomas, the prevalence of oral exposure to medroxyprogesterone acetate was similar between cases (2.38%) and controls (2.29%). In both crude and adjusted models, medroxyprogesterone acetate exposure was not associated with being a case (adjusted OR 0.97, 95% CI 0.93–1.01); this null association persisted across all duration categories. The prevalence of injection exposure to medroxyprogesterone acetate was nearly twice as high among cases (0.67%) than controls (0.39%); medroxyprogesterone acetate exposure was associated with 76% increased odds of being a case (OR 1.76, 95% CI 1.63–1.90), an association that persisted in the adjusted model (OR 1.53, 95% CI 1.40–1.67). There was evidence of increased odds by duration of exposure (linear trend, $p < 0.0001$). This association was notably specific to injection exposure to medroxyprogesterone acetate and cerebral meningiomas. No association was observed for oral medroxyprogesterone acetate exposure or for spinal meningiomas (for both oral and injection medroxyprogesterone acetate exposure).

5.2 Pharmacokinetic properties

Absorption

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high inter-individual variability in serum levels after standard doses given by either route of administration.

Biotransformation

MPA is metabolised and conjugated in the liver.

Elimination

Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Acute toxicity

The oral LD_{50} of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD_{50} in the mouse was 6985 mg/kg.

Subacute and chronic toxicity

MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5 mg, 5 mg and 10 mg tablets:

Calcium stearate,
Lactose monohydrate,
Liquid paraffin,
Maize starch,
Purified talc,
Purified water,
Sucrose,
Sunset yellow FCF (2.5 mg tablets only),
Indigo carmine (5 mg tablets only).

PROVERA 100 mg and 200 mg tablets:

Docusate sodium,
Hydrolysed gelatin,
Isopropyl alcohol,
Macrogol 400,
Magnesium stearate,
Maize starch,
Microcrystalline cellulose,
Purified water,
Sodium benzoate,
Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 mg, 5 mg, 10 mg tablets: 5 years

100 mg, 200 mg tablets: 3 years

6.4 Special precautions for storage

2.5 mg, 5 mg and 10 mg tablets: Store at or below 30°C.

100 mg and 200 mg: Store at or below 25°C.

6.5 Nature and contents of container

2.5 mg tablets are supplied as blister packs of 30 and 56 tablets.

5 mg tablets are supplied in blister packs and glass bottle of 100 tablets.

10 mg tablets are supplied in blister packs.

100 mg tablets are supplied in blister packs and glass bottle of 100 tablets.

200 mg tablets are supplied as blister packs and bottle of 30 tablets.

Not all strengths and pack sizes are available.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363
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9. DATE OF FIRST APPROVAL

13 November 1990 (2.5 mg),

03 May 1988 (5 mg, 10 mg)

31 December 1969 (100 mg, 200 mg)

10. DATE OF REVISION OF THE TEXT

3 October 2025

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 & 5.1	Addition of new information regarding meningioma
2, 4.4 & 4.9	Minor editorial changes