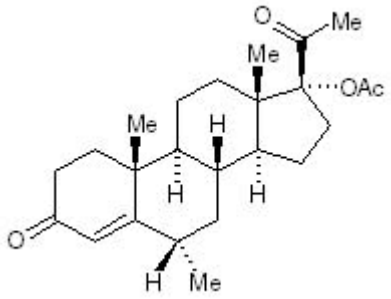
PRODUCT INFORMATION

MEDROXYPROGESTERONE SANDOZ 10 mg TABLETS

NAME OF THE MEDICINE

6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate
Medroxyprogesterone acetate



CAS [71-58-9] $C_{24}H_{34}O_4$ 386.5

DESCRIPTION

A white or almost white, crystalline powder, practically insoluble in water, soluble in acetone, sparingly soluble in alcohol and in methanol, slightly soluble in ether.

In addition to medroxyprogesterone acetate, Medroxyprogesterone Sandoz tablets contain:
starch-maize, sodium starch glycollate, lactose monohydrate, cellulose-microcrystalline, silica-colloidal anhydrous, magnesium stearate.

PHARMACOLOGY

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

Human. Medroxyprogesterone acetate is a progestational agent. When administered in recommended doses to women with adequate endogenous oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation. Like progesterone, medroxyprogesterone acetate 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.

Pharmacokinetics

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

Medroxyprogesterone acetate is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

Medroxyprogesterone acetate is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine as both conjugated and free forms.

Toxicology

Animal toxicology. Acute toxicity.

The oral LD50 of medroxyprogesterone acetate was found to be greater than 10,000 mg/kg in the mouse. The intraperitoneal LD50 in the mouse was 6,985 mg/kg.

Subacute and chronic toxicity. Medroxyprogesterone acetate administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be nontoxic. Medroxyprogesterone acetate was administered orally to dogs and rats at 3, 10 and 30 mg/kg/day for six months. The drug was considered to be nontoxic at these levels but with anticipated hormonal effects at the higher dose.

Reproduction studies. Medroxyprogesterone acetate 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.

Carcinogenesis and mutagenesis. Long-term toxicology studies in the monkey, dog and rat with parenteral medroxyprogesterone acetate have disclosed the following.

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for seven 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 two high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for ten 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 ten 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 three 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 two years.

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

CLINICAL TRIALS

Bone mineral density changes

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

However, a clinical study of adult women of childbearing potential given medroxyprogesterone acetate (MPA) 150 mg by intramuscular (IM) injection every three months, for contraception, demonstrated an average decrease of 5.4% in lumbar spine BMD over five years, with at least partial recovery of this bone loss during the first two years after treatment was discontinued. A similar clinical study of MPA 150 mg IM injection every three months in adolescent females, for contraception, demonstrated similar decreases in BMD, which were also more pronounced during the first two years of treatment and which again were at least partially reversible when treatment was discontinued. Decreases in serum oestrogen due to medroxyprogesterone acetate may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life (see WARNINGS).

INDICATIONS

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with medroxyprogesterone acetate.

Abnormal uterine bleeding in the absence of organic pathology.

Adjunct to oestrogen therapy in women with an intact uterus.

CONTRAINDICATIONS

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 medroxyprogesterone acetate or to any excipients.
Known or suspected pregnancy(see PRECAUTIONS).
Severe uncontrolled hypertension.
Known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

The doctor 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.

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.

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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

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. Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT 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.

Current use of oestrogen only or oestrogen plus progestin products in post-menopausal women for five or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined oestrogen/ progestin 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. HRT in postmenopausal women is not generally appropriate for long-term use and should not be prescribed for longer than six months without re-examining the patient.

<u>Effects on laboratory tests:</u>

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

- gonadotrophin levels;
- plasma progesterone levels;
- urinary pregnanediol levels;
- plasma testosterone levels (in the male);
- plasma oestrogen 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.

Decrease in bone mineral density

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given medroxyprogesterone acetate 150 mg IM (intramuscularly) every three months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to medroxyprogesterone acetate may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use medroxyprogesterone acetate long-term. It is recommended that all patients have adequate calcium and vitamin D intake.

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with an HRT regimen of conjugated oestrogens and medroxyprogesterone acetate. 85% of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

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 medroxyprogesterone acetate 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. Nonfunctional 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 progestogen therapy when relevant specimens are submitted.

Weight gain may be associated with the use of medroxyprogesterone acetate. 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 medroxyprogesterone acetate 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.

With the exception of anamnestic endometriosis, use of gestagen is not recommended in women without intact uterus.

Use in Pregnancy: (Category D)

Medroxyprogesterone acetate tablets are not to be used as a test for pregnancy or where pregnancy is suspected. If medroxyprogesterone acetate is used during pregnancy, or if the patient becomes pregnant while using medroxyprogesterone acetate, the patient should be apprised of the potential risk to the fetus (see CONTRAINDICATIONS).

Animal studies have shown that high doses of progestogens can cause masculinisation of the female foetus. 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.

Note. In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of hormone replacement therapy (HRT). An endometrial biopsy may be performed at the discretion of the attending doctor.

Dementia
In a study of women 65 years of age and older (a randomised controlled sub-study of the Women's Health Initiative, the Women's Health Initiative Memory Study; n=4,532, 54% older than 70), those treated with 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. After an average follow-up of 4 years, the absolute risk of probable dementia was 45 per 10,000 women-years in the placebo

group. It is unknown whether these findings apply to younger postmenopausal women. Therefore, in the older women, the use of Medroxyprogesterone Sandoz for the prevention of osteoporosis should only be considered for those who have failed on, or were intolerant of, non-oestrogen medication.

Hormone therapy for the prophylaxis of dementia or mild cognitive impairment is not recommended.

Ovarian carcinoma
The conjugated equine estrogens/medroxyprogesterone acetate sub-study revealed that estrogen plus gestagen increased the risk of ovarian carcinoma, but the increase was not statistically significant.

INTERACTIONS WITH OTHER MEDICINES

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

The need for insulin or oral antidiabetics can be changed due to an influence on glucose tolerance.

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 of CYP3A4 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 with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

Combination hormone replacement therapy should only be used in non-hysterectomised women (see PRECAUTIONS).

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

Hypersensitivity. Anaphylaxis and anaphylactoid-like reactions, angioedema.

Cardiovascular. Cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, retinal thrombosis, tachycardia, thromboembolic disease, thrombophlebitis, pulmonary embolism.

Central nervous system. Confusion, loss of concentration, euphoria, vision disorders, dementia, nervousness, insomnia, somnolence, fatigue, depression, dizziness and

headache, and tremor. Some patients may complain of premenstrual-like depression while on medroxyprogesterone acetate.

Dermatological. Urticaria, pruritus, rash, acne, hirsutism, alopecia and sweating.

Genitourinary. Irregular uterine bleeding (increase, decrease), spotting and amenorrhoea, prolonged anovulation.

Gastrointestinal/ hepatobiliary. Nausea, vomiting, constipation, diarrhoea, cholestatic icterus, dry mouth, disturbed liver function, jaundice.

Metabolic and nutritional. Adrenergic-like effects (e.g. fine hand tremors, cramps in calves at night), corticoid-like effects (e.g. Cushingoid syndrome), decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria.

Breast. Tenderness and galactorrhoea, mastodynia. The use of oestrogens and progestogens by postmenopausal women has been associated with an increased risk of breast cancer (see WARNINGS).

Cervix. Cervical erosions, changes in excretions and secretions.

Other. Changes in appetite, changes in libido, oedema/fluid retention, hyperpyrexia, weight change, malaise, hypercalcaemia.

Moderate elevation of blood pressure, transient elevation of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts.

Post-marketing experience**:** There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

DOSAGE AND ADMINISTRATION

Endometriosis. Beginning on the first day of the menstrual cycle, Medroxyprogesterone Sandoz 10 mg three times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy. In amenorrhoea associated with a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with Medroxyprogesterone Sandoz 10 mg daily for ten days; 10 mg daily for five to ten days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for three consecutive cycles.

Abnormal uterine bleeding in the absence of organic pathology. 10 mg daily for five to ten days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for three consecutive cycles.

Adjunct to oestrogen therapy. 10 to 20 mg daily for at least ten days of each cycle. Use of combined oestrogen/ 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 woman, and should be periodically evaluated. HRT in postmenopausal women is not generally appropriate for long-term use and should not be prescribed for longer than six months without re-examining the patient.

Note: Medroxyprogesterone Sandoz 10 mg tablets should not be broken or crushed.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Oral doses up to 3 g/day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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 doctor should carefully observe the patient for the potential side effects.

Treatment
Overdose treatment is symptomatic and supportive.

PRESENTATION AND STORAGE CONDITIONS

Medroxyprogesterone Sandoz 10 mg tablets are round tablets, scored on one side.
They are available in PVC/PVDC blister of 30 or 100* tablets per carton.

Store below 25°C.
Protect from light.

*Not currently marketed in Australia

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 19/07/2001

Date of most recent amendment: 16/01/2017s