For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

HerNMP

(Progesterone Injection I.P.)

COMPOSITION

Each ml contains:

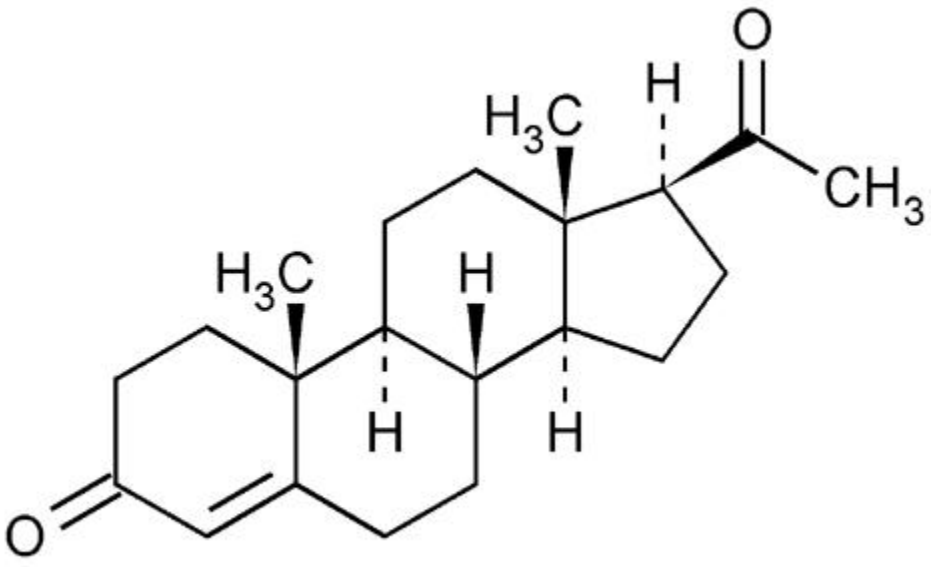
Progesterone I.P. 50mg

Benzyl Alcohol I.P. 10%w/v

Ethyl Oleate I.P .q.s.

DESCRIPTION

Progesterone occurs as White or almost white, crystalline powder or colourless crystals.. It is odorless and is stable in air. Practically insoluble in water, freely soluble in ethanol, sparingly soluble in acetone and in fatty oils. It has the following structural formula:



It is having the empirical formula of $C_{21}H_{30}O_2$ and molecular weight of 314.5.

Chemically Progesterone is Pregn-4-ene-3, 20-Dione.

CLINICAL PHARMACOLOGY

Mechanism of Action

Transforms proliferative endometrium into secretory endometrium. Inhibits (at the usual dose range) the secretion of pituitary gonadotropins, which in turn prevents follicular aturation and ovulation.

Pharmacokinetics

Absorption:

After intramuscular administration of 10 mg of progesterone in oil maximum plasma concentrations (geometric mean of 7 ng/mL) were reached within approximately 8 hours after injection and plasma concentrations remained above baseline for about 24 hours after injection. Injection of 10, 25, and 50 mg resulted in geometric mean values for maximum plasma concentration (CMAX) of 7, 28, and 50 ng/mL, respectively.

Distribution:

Progesterone is extensively bound to plasma proteins, primarily albumin (50 to 54%) and cortisol-binding protein (43 to 48%).

Metabolism:

Progesterone is metabolized primarily in the liver by reduction to pregnanediol, pregnanetriol and pregnanolone. Subsequent conjugation results in the formation of glucuronide and sulfate metabolites. The mean plasma metabolic clearance rate in cycling women is 2510 ± 135 (SEM) L/day.

Excretion:

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the urine and bile. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

The pharmacokinetic data was determined in a small number of patients, limiting the precision in which population values may be estimated.

Special Populations

Renal Insufficiency:

The safety and effectiveness in patients with renal insufficiency have not been established. Since progesterone metabolites are excreted mainly by the kidneys, progesterone should be administered with caution and careful monitoring in this patient population.

Hepatic Insufficiency:

The safety and effectiveness in patients with hepatic insufficiency have not been established. Since progesterone is metabolized by the liver, use in patients with liver dysfunction or disease is contraindicated.

Drug Interactions

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 < 01 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4 and these data suggest that ketoconazole or other known inhibitors of this enzyme may increase the bioavailability of progesterone. The clinical relevance of the in vitro findings is unknown.

INDICATIONS

This drug is indicated in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

CONTRAINDICATION

- Current or past history of thrombophlebitis, thromboembolic disorders, or cerebral apoplexy.
- Liver dysfunction or disease.
- Known or suspected malignancy of breast or genital organs.
- Undiagnosed vaginal bleeding.
- Missed abortion.

- Known sensitivity to progesterone injection, USP.

WARNINGS AND PRECAUTIONS

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 or be suspected, the drug should be discontinued immediately.

Medication should be discontinued pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

General

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear.

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

In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind, and adequate diagnostic measures undertaken.

Patients who have a history of psychic 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 progestin may mask the onset of the climacteric.

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

There are possible risks which may be associated with the use of progestin treatment, including adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects.

A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term intramuscular administration of Medroxyprogesterone acetate (MPA) has been shown to produce mammary tumors in beagle dogs. There is no evidence of a carcinogenic effect associated with the oral administration of MPA to rats and mice.

Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Progesterone at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

Geriatric Use

The safety and effectiveness in geriatric patients (over age 65) have not been established.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Nursing Mothers

Detectable amounts of drug have been identified in the milk of mothers receiving progestational drugs. The effect of this on the nursing infant has not been determined.

ADVERSE EFECTS

Breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; edema; change in weight (increase or decrease); changes in cervical erosion and cervical secretions; cholestatic jaundice; breast tenderness and galactorrhea; pain, irritation, and/or redness at

the injection area; skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash; acne, alopecia and hirsutism; rash (allergic) with and without pruritus; anaphylactoid reactions; mental depression; pyrexia; insomnia; nausea; and somnolence.
A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed. There is also evidence suggestive of an association with neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs: Rise in blood pressure in susceptible individual, premenstrual syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, and dizziness.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs: increased sulfobromophthalein retention and other hepatic function tests; coagulation tests: increase in prothrombin factors VII, VIII, IX, and X; metyrapone test; pregnanediol determinations; thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

DOSAGES AND ADMINISTRATION

Progesterone injection is administered by intramuscular injection. It differs from other commonly used steroids in that it is irritating at the place of injection.

Amenorrhea:

Five to 10 mg are given for six to eight consecutive days. If there has been sufficient ovarian activity to produce a proliferative endometrium, one can expect withdrawal bleeding forty-eight to seventy-two hours after the last injection. This may be followed by spontaneous normal cycles.

Functional Uterine Bleeding:

Five to 10 mg are given daily for six doses. Bleeding may be expected to cease within six days. When estrogen is given as well, the administration of progesterone is begun after two weeks of estrogen therapy. If menstrual flow begins during the course of injections of progesterone, they are discontinued.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

EXPIRY DATE:

Do not use later than the date of expiry

STORAGE:

Store below 30°c, Protected from light.

PRESENTATION:

HerNMP injection is available as 2ml ampoule.

MARKETED BY:

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