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

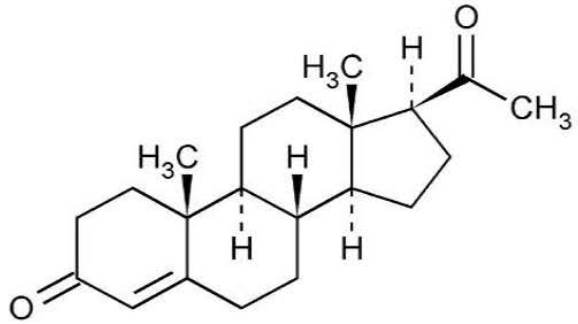
herNMP SR
(Progesterone Sustained Release Tablets)

COMPOSITION
herNMP SR 200
Each film coated sustained release tablet contains:
Progesterone I.P. 200 mg (Natural Micronized)
Excipients q.s.
Color: Titanium Dioxide I.P.

herNMP SR 300
Each film coated sustained release tablet contains:
Progesterone I.P. 300 mg (Natural Micronized)
Excipients q.s.
Color: Titanium Dioxide I.P.

herNMP SR 400
Each film coated sustained release tablet contains:
Progesterone I.P. 400 mg (Natural Micronized)
Excipients q.s.
Color: Quinoline Yellow Lake

DESCRIPTION:
Progesterone has a molecular weight of 314.47 and a molecular formula of $C_{21}H_{30}O_2$. Progesterone (pregn-4-ene-3, 20-dione) is a white or creamy white, odorless, crystalline powder practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils, stable in air, melting between 126° and 131°C. The structural formula is:



CLINICAL PHARMACOLOGY
MECHANISM OF ACTION
Progesterone is lipophilic in nature and diffuse freely into cells, where they bind to the progesterone receptors and exert their progestational activity. The steroid receptor complex binds to DNA in the nucleus, thereby inducing the synthesis of specific proteins. Progesterone receptor concentrations are low in absence of estrogens and increase following estrogen administration.

Pharmacokinetics

Absorption:

The Micronized progesterone is absorbed through the digestive tract. herNMP SR is a sustained release formulation of Micronized progesterone . The absolute bioavailability of micronized progesterone is not known.

Distribution:

Circulating progesterone is extensively bound to plasma proteins, especially albumin and corticosteroid binding globulin.

Metabolism:

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation and epimerization.

Excretion:

The glucuronide and sulfate conjugates of pregnanediols and pregnanolones are excreted primarily in urine. A smaller quantity is excreted in bile. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

Special population:

The Pharmacokinetics of progesterone has not been assessed in low body weight or in obese patients Hepatic and renal insufficiency.

Indications

Disorders associated with deficiency of progesterone, in particular:

- Menopause (In addition to estrogenic treatment) to significantly reduce the risk of endometrial hyperplasia and carcinoma.
- Premenstrual syndrome
- Menstrual irregularities through dysovulation or anovulation
- Benign mastopathies
- Premenopause
- Prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets.
- Secondary amenorrhea

DOSAGE AND ADMINISTRATION:

On an average in the case of deficiency of progesterone, the dosage is from 200 to 300 mg of progesterone per day once daily or in two divided doses, one in the morning and one at night. It is recommended to use the tablet at intervals of one hour before or after meals. The evening dose/once daily is preferably taken at night at the time of going to bed.

Menopause (In addition to estrogen treatment)

One tablet of 200 mg per day in the evening for the last 14 days of estrogen treatment per cycle (i.e. from day 8 to day 21 for a 28 day cycle and from day 12 to day 25 for a 30 day cycle). With high dosage of estrogen should be administered 300 mg daily.

Premenstrual syndrome, benign mastopathies, menstrual irregularities, pre-menopause
The treatment will be started at a dose of 200 mg to 300 per day, 10 days per cycle, usually from 14th day to until onset of menstruation.

Prevention of Endometrial Hyperplasia
It should be given as a single daily dose at bedtime, 200 mg orally for 12 days sequentially per 28-day cycle, to a postmenopausal woman with a uterus who is receiving daily conjugated estrogens tablets.

Treatment of secondary amenorrhea
It may be given as a single daily dose of 400 mg at bedtime for 10 days.

CONTRAINDICATIONS:
Progesterone should not be used in women with any of the following conditions:

- Known, suspected, or history of breast cancer
- Active deep vein thrombosis, pulmonary embolism or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions
- Known or suspected pregnancy
- Serious alterations in hepatic functions.

WARNINGS

- Progesterone hormone is present in significant concentrations in women during second half of menstrual cycle and during pregnancy. This should be borne in mind when treating patients with conditions that may be hormone sensitive.

- Progesterone is not a treatment against the risk of premature labour pains; the administration of micronized progesterone during the second and third trimester of pregnancy may result in appearance of severe cholestasis or hepatitis.

- More than half of the spontaneous premature abortions are due to genetic abnormalities. Further infectious phenomena and mechanical troubles can be responsible for abortions.

- In case of drowsiness after 1 to 3 hours of oral administration, the dosage may be reduced or the patient may be shifted to once daily evening dose or adopt vaginal route (herNMP soft gelatin capsule).

- In case of shortening of menstrual cycle or intermittent bleeding shift the initiation of treatment to a later date (e.g. 19th day of cycle instead of 17th day).

- Attention is drawn, particularly in case of people who drive vehicles or operate machines, to the fact that there is risk of drowsiness or giddiness associated with the use of this medicine.

Other important warnings

1. Cardiovascular disorders

An increased risk of pulmonary embolism, deep vein thrombosis (DVT), stroke, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

A. Stroke

In the Women's Health Initiative (WHI) estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

B. Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1 and a trend toward decreasing relative risk was reported in years 2 through 5.

C. Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens with progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

A. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nCI, 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo.

Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same sub study, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogenalone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

B. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

C. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent nCI, 0.77 – 3.24). The absolute

risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable dementia
In the estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women.

4. Vision abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogen. Discontinue estrogen plus progestin therapy 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 papilledema or retinal vascular lesions, estrogen plus progestin therapy should be permanently discontinued.

PRECAUTIONS
A. General
1. Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include an increased risk of breast cancer.

2. Fluid Retention
Progesterone may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation.

3. Dizziness and Drowsiness
Progesterone may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery. Progesterone should be taken as a single daily dose at bedtime.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary

carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Pregnancy and lactation:
Progesterone should not be used during pregnancy.
Pregnancy Category B:
Reproductive studies have been performed in mice at doses up to 9 times the human oral dose, in rats at doses up to 44 times the human oral dose, in rabbits at a dose of 10 mcg/day delivered locally within the uterus by an implanted device, in guinea pigs at doses of approximately one-half the human oral dose and in rhesus monkeys at doses approximately the human dose, all based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

The administration of this medicine in the course of the second and third trimester of pregnancy can favour the appearance of severe cholestasis or hepatitis.

Nursing Women
Detectable amounts of progestin have been identified in the milk of nursing women receiving progestins. Caution should be exercised when Progesterone administered to a nursing woman.

Pediatric Use
Progesterone is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use
There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Progesterone to determine whether those over 65 years of age differ from younger subjects in their response to Progesterone.

Drug interactions
The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 < 0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4, hence 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.

ADVERSE EFFECTS:

See Warning and Precautions

The menstrual cycle may be shortened or there may by inter-menstrual bleeding. Menstruation may occur earlier than expected, or more rarely menstruation may be delayed.

Oral route: Drowsiness or giddiness arising 1 to 3 hours after ingestion of the product.

Postmarketing Experience:
The following additional adverse reactions have been reported with Progesterone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Genitourinary System: endometrial carcinoma, hypospadia, intra-uterine death, menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst, spontaneous abortion.

Cardiovascular: circulatory collapse, congenital heart disease (including ventricular septal defect and patent ductus arteriosus), hypertension, hypotension, tachycardia.

Gastrointestinal: acute pancreatitis, cholestasis, cholestatic hepatitis, dysphagia, hepatic failure, hepatic necrosis, hepatitis, increased liver function tests (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased), jaundice, swollen tongue.

Skin: alopecia, pruritus, urticaria

Eyes: blurred vision, diplopia, and visual disturbance.

Central Nervous System: aggression, convulsion, depersonalization, depressed consciousness, disorientation, dysarthria, loss of consciousness, paresthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack, suicidal ideation.

During initial therapy, a few women have experienced a constellation of many or all of the following symptoms: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confusion, disorientation, feeling drunk, and shortness of breath.

Miscellaneous: abnormal gait, anaphylactic reaction, arthralgia, blood glucose increased, choking, cleft lip, cleft palate, difficulty walking, dyspnea, face edema, feeling abnormal, feeling drunk, hypersensitivity, asthma, muscle cramp, throat tightness, tinnitus, vertigo, weight decreased, weight increased.

OVERDOSAGE:

There is a wide margin of safety with progesterone, but over dosage may produce euphoria or dysmenorrhoea. No studies on overdosage have been conducted in humans. In the case of over dosage, it should be discontinued and the patient should be treated symptomatically.

EXPIRY

Do not use later than the date of expiry.

STORAGE
Store at a room temperature, Protected from light and moisture.

PRESENTATION:
herNMP SR 200, 300 and 400 are available in Blister strip of 10 Tablets

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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Ahmedabad-380 009, INDIA

IN/HerNMP SR 200,300,400mg/JUL-16/01/PI