PRODUCT INFORMATION
Oripro® Progesterone 100mg and 200mg Pessaries

NAME OF THE MEDICINE
Oripro® Progesterone 100mg and 200mg Pessaries

Chemical Name: Pregn-4-ene-3,20-dione.
Structural Formula:

![Structural Formula]

Molecular Formula: C_{21}H_{30}O_{2}
Molecular weight: 314.5
CAS registry number: 57-83-0

DESCRIPTION
Oripro contain as active substance 100mg or 200mg of progesterone (micronized) in hard fat.

PHARMACOLOGY
Pharmacokinetics
Absorption:
Progesterone is rapidly absorbed following vaginal administration. The time to peak plasma level varies depending on the individual and the dose administered. In general peak plasma levels are reached within 3-8 hours with a decrease in levels over 24 hours.

Distribution:
Progesterone is extensively protein bound (96-99%), principally to serum albumin and corticosteroid binding globulin.

Metabolism:
Progesterone is extensively metabolized (conjugated) by the liver, to largely pregnanediols and pregnanolones. Orally taken progesterone has a short half-life and is rapidly cleared from the peripheral circulation because of this first past metabolism effect. However prolonged
serum levels result from vaginal or rectal administration because absorption and action occur before biotransformation of it by the liver.

**Excretion:**
Progesterone is primarily excreted renally (50 to 60%) as pregnanediol or the pregnanediol conjugate with minimal (10%) biliary and faecal excretion.

**Pharmacodynamics**
Progesterone is a naturally occurring female sex hormone secreted by the ovary, placenta and adrenal gland. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase. In normal physiological conditions if a released mature ovum is not fertilised a sudden decline in the release of progesterone from the corpus luteum occurs, usually at the end of the cycle. However, if fertilisation occurs progesterone is continued to be secreted and the increased level sustains the endometrium and maintains the pregnancy.

**INDICATIONS**
Assisted reproductive technology treatment of infertile women with progesterone deficiency, requiring progesterone supplementation or replacement to support embryo implantation and maintain initial pregnancy.

**CONTRAINDICATIONS**
Sensitivity to progesterone, sensitivity to hard fat, undiagnosed vaginal bleeding, undiagnosed urinary tract bleeding, liver dysfunction or disease, active thrombophlebitis or thromboembolic disorder (deep vein thrombosis, pulmonary embolism) or a history of hormone associated thrombophlebitis or thromboembolic disorder, pregnancy (when normal progesterone levels are present), known or suspected malignancy of the breast or genital organs, missed abortion.

**PRECAUTIONS**
Before initiation or recommencing progesterone therapy in women, a physical examination should be performed, including special attention to the breasts, abdomen and pelvic organs and a Papanicolaou (Pap) smear.

*Use with caution and careful monitoring in the following:*
Conditions that might be aggravated by fluid retention (e.g. asthma, seizure disorders, migraine, or cardiac or renal dysfunction).
History of mental depression; discontinue if serious depression recurs during therapy.
Diabetic patients as high doses of progesterone therapy can lower glucose tolerance in some patients.
History of hepatic disease or dysfunction as progesterone is metabolized in the liver.
Hyperlipidemia as progesterone may increase low density lipoprotein (LDL) and lower high density lipoprotein (HDL) levels and aggravate problems in controlling hyperlipidemia.
Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.
Use in Pregnancy

Category A.
Progesterone crosses the placenta. No association has been found between the maternal use of progesterone in early pregnancy and foetal malformations. Data on the risk of foetal effects with exposure in later stages of pregnancy are limited. Male and female genital abnormalities (hypospadias and virilisation) have been observed in foetuses of animals treated with progesterone during gestation.

Use in Lactation

Progesterone is excreted into human milk and at supraphysiological levels may affect the quantity of the breast milk. The effect of exogenous progesterone on breast-feeding infants have not been adequately determined in humans.

Carcinogenicity

No study has been conducted to specifically examine the genotoxic potential of progesterone. Animal studies showed that progesterone was able to induce and/or promote the formation of mammary, uterine, ovarian, endometrial, cervical and vaginal tumours. The clinical relevance of these findings in animals remains unclear.

Interactions with other medicines

Potentially clinical significant interactions with progesterone, may occur with any of the following medications depending on, amount present. Hepatic enzyme inducing medications, such as Carbamazepine, Phenobarbitone, Phenytoin, Rifabutin, Rifampicin, may decrease the efficacy of progesterone because of the enhanced liver metabolism caused by these drugs. Aminoglutethimide may significantly lower serum concentrations of progesterone by an undetermined mechanism.

Effects on clinical, laboratory or other tests

Potentially clinical significant alterations to laboratory test results/values can occur with the following tests:
Biopsy - (pathologist should be notified of relevant specimens).
Glucose tolerance test - (varies with progestogens and dose, glucose tolerance may be increased or decreased).
Metyrapone - (lower response than normally expected).

Effects on Diagnostic tests

Apolipoprotein A, HDL, LDL and Total cholesterol and Triglycerides - (serum concentrations may be increased or decreased and may differ depending on type of progestogen, dose, dosing, and duration of therapy).
Liver, thyroid and other endocrine function tests may be affected by progesterone.
Coagulation tests: Prothrombin, clotting factors II, VII, VIII, IX, and X - (serum concentrations may be increased).
ADVERSE EFFECTS
As Progesterone pessaries are being absorbed by mucosal surfaces local irritation or itching may occur in sensitive persons at initiation of treatment, in general this is of a transient nature.

Common (usually dose related)
Reproductive, Female: Amenorrhoea, abnormal breakthrough uterine bleeding or metromenorrhagia, spotting, changes in cervical eversion and secretions.
Metabolic and Nutritional: Hyperglycaemia (dry mouth, frequent urination, loss of appetite, unusual thirst).

Uncommon
Reproductive, Female: Galactorrhoea.
Psychiatric: Mental depression.
Skin and Appendages: Skin rash, Pruritus.

Rare
Endocrine: Adrenal suppression or insufficiency (causing symptoms of dizziness, nausea or vomiting, unusual tiredness or weakness).
Circulatory System: Thromboembolism or thrombus formation (causing headache or migraine, loss of or change of speech, coordination or vision, pain or numbness in chest, arm or leg; unexplained shortness of breath).
For further information see sections Contraindications and Precautions

Other
The following additional reactions indicate need for medical attention only if they continue or are troublesome.

Incidence more frequent:
Body as a Whole: Abdominal cramping, bloating, oedema (swelling face, ankles and feet), unusual tiredness or weakness or weight gain, pain, itchiness or irritation at site of insertion.
Central and Peripheral Nervous System: Headache, dizziness, and drowsiness.
Reproductive, Female: Ovarian enlargement or ovarian cyst formation (abdominal pain), Moniliasis Genital.

Incidence less frequent:
Body as a Whole: Acne, breast pain or tenderness, hot flushes.
Skin and Appendages: Loss or gain of body facial or scalp hair or melasma (brown spots on exposed skin).
Central and Peripheral Nervous System: Insomnia
Gastrointestinal system: Nausea.
Circulatory System: Increased blood pressure in susceptible individuals.
Psychiatric: Mild mood changes, nervousness, changes in libido.

DOSAGE AND ADMINISTRATION
Adult Dosage:
Usual dosage is 200mg daily to a maximum of 400mg twice a day. Dosage in assisted reproductive technology (corpus luteum insufficiency) is 25mg to 100mg one to two times a day initiated within several days of ovulation. Treatment duration is usually continued if the patient is pregnant, up to about the eleventh week of gestation.
Other intravaginal therapies should not be used while progesterone pessary treatment is being undertaken.

A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be omitted and the regular dosing regimen continued. **Patient Instructions:** The pessary should be removed from its wrapper and inserted deep into the vagina, while either in a squatting position or lying on back or side. If a daily dose is being administered then a preferable time of dosing is at night before retiring.

**Paediatric Dosage:** Not recommended.

**OVERDOSAGE**

**Symptoms**
Overdosage with Oripro after vaginal administration is unlikely. If large quantities of pessaries are ingested, euphoria, or nausea, vomiting or dysmenorrhoea may develop.

**Treatment**
No specific antidote is known. Symptomatic and supportive treatment can be given if necessary.

**PRESENTATION AND STORAGE CONDITIONS**
Opaque, bullet-shaped waxy, solid masses, containing 100mg or 200mg progesterone supplied as:
- 15 individually wrapped pessaries in a glass jar (not currently marketed).
- Blisters in a unit carton containing 5 (samples), 15 or 30 pessaries (not all pack sizes may be marketed).

Store below 25°C.

**NAME AND ADDRESS OF THE SPONSOR**
Orion Laboratories Pty Ltd T/A Perrigo Australia
25 – 29 Delawney Street
Balcatta
Western Australia
6021

**POISONS SCHEDULE OF THE MEDICINE**
S4: Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS**
December 2003

**DATE OF MOST RECENT AMENDMENT:**
27 September 2016