NAME OF THE MEDICINAL PRODUCT

Primolut Depot, 250mg, solution for intramuscular injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Primolut Depot contains 250 mg hydroxyprogesterone caproate in oily solution.

PHARMACEUTICAL FORM

Oily solution for intramuscular injection.

CLINICAL PARTICULARS

Therapeutic indications

Habitual and imminent abortion, infertility due to corpus luteum insufficiency, primary and secondary amenorrhea.

Dosage and method of administration

How to use Primolut Depot

Primolut Depot must be administered always as a deep intramuscular injection, preferably intragluteal, alternatively into the upper arm. The injection must be administered extremely slowly (see section 4.8 “Undesirable effects“). It is advisable to place a plaster over the injection site after the injection to prevent any reflux of the Primolut Depot solution.

Abortion

According to the present state of scientific knowledge, medicinal therapy should be given in early pregnancy only if it is absolutely essential. This is also valid for the use of hormone preparations such as Primolut Depot for the maintenance of pregnancy. Consequently, Primolut Depot should only be prescribed if there is an urgent desire for children - primarily in the presence of corpus luteum insufficiency or a case history of abortion.

Primolut Depot is indicated for both prophylaxis and treatment of abortion because it compensates for the hormone deficit, induces quiescence of the uterus and stimulates growth of an underdeveloped uterus.

Prolonged treatment with an adequate dosage of Primolut Depot is necessary to achieve this objective and to maintain pregnancy.

Because Primolut Depot places the uterus at rest, it is possible for an already dead embryo to be retained. In the case of protracted therapy, it is therefore necessary to check the continued existence of pregnancy by means of appropriate examinations and immunological tests.

Habitual abortion

As soon as pregnancy has been confirmed by diagnosis, 250 - 500 mg Primolut Depot are injected i.m. at weekly intervals during the initial months or, in individual cases, for even longer.

Imminent abortion

The therapy is initiated with an i.m. injection of 500 mg Primolut Depot 2 - 3 times weekly until the bleeding ceases, bed rest being urgently recommended. The treatment must then be continued for several weeks with 250 mg Primolut Depot i.m. twice weekly until the patient remains free from complaints and bleeding despite mobilization. Whether Primolut Depot should be given prophylactically even beyond this point will depend on the individual case.

8 to 14 days after unsuccessful treatment of imminent abortion and subsequent curettage withdrawal bleeding may occur in isolated cases owing to the continuing effect of Primolut Depot which subsides only gradually. However, no further measures are necessary.

Infertility due to corpus luteum insufficiency

In cases in which the luteal phase is short - a situation characterized by a too short-lived increase in the basal body temperature in the second half of the cycle - Primolut Depot brings about secretory transformation of the inadequately transformed endometrium, thus improving the chances of nidation.

Intramuscular injection of 250 mg Primolut Depot should be given about 3 days after the rise in basal body temperature. Since there is often a coexisting estrogen deficit, endometrial priming with an estrogen should be carried out (e.g., for 14 days) before beginning treatment with Primolut Depot. Thus a physiological transformation of the endometrium can be achieved.

Primary and secondary amenorrhea

Hormone treatment of secondary amenorrhea can be carried out only after the exclusion of pregnancy.

Before treatment of primary or secondary amenorrhea is commenced the presence of a prolactin-producing pituitary tumor should be excluded. The possibility cannot be ruled out that macroadenomas increase in size when exposed to high doses of estrogen for prolonged periods of time.

Endometrial priming with an estrogen should be carried out (e.g., for 14 days) before beginning treatment with Primolut Depot. Thereafter, treatment is commenced with 250 mg Primolut Depot intramuscularly.

In patients in whom sufficient endogenous estrogen levels have been achieved, an attempt can be made to stop the estrogen treatment and to induce cyclical bleeding by administering 250 mg Primolut Depot intramuscularly between the 18th and the 20th day of the cycle.

Please note:

If there is no desire for children, contraception should be practiced with non-hormonal methods (with the exception of the rhythm and temperature methods). If withdrawal bleeding at regular intervals of about 28 days fails to occur under the therapeutic scheme pregnancy must be considered despite the protective measures. The treatment must then be interrupted until the situation has been clarified by differential diagnosis.

If, on the other hand, there is a desire for children and pregnancy has occurred, treatment with Primolut Depot should only be continued if there is reason to assume a risk of abortion.

Contraindications

Primolut Depot should not be used in the presence of any of the conditions listed below, which are derived also from information on other progestogen-only products. Should any of the conditions appear during the use of Primolut Depot, the use of the preparation must be discontinued immediately.

Active venous thromboembolic disorders

Arterial and cardiovascular disease present or in history (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease)

Diabetes mellitus with vascular involvement

Presence or history of severe hepatic disease as long as liver function values have not returned to normal

Presence or history of liver tumors (benign or malignant)

Known or suspected sex hormone-dependent malignancies

Hypersensitivity to hydroxyprogesterone caproate or to any of the excipients

Special warnings and special precautions for use

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Primolut Depot is started or continued.

Circulatory disorders

It has been concluded from epidemiological surveys that the use of oral estrogen/progestogen containing ovulation inhibitors is attended by an increased incidence of thromboembolic diseases. Therefore, one should keep the possibility of an increased thromboembolic risk in mind, particularly where there is a history of thromboembolic diseases.

Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumors

In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of hormonal substances such as the one contained in Primolut Depot. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking Primolut Depot.

Other conditions

Strict medical supervision is necessary if the patient suffers from diabetes.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation when taking Primolut Depot **.**

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

Medical examination

A complete medical history should be taken and a physical and gynecological examination should be performed prior to the initiation or reinstitution of the use of Primolut Depot, guided by the contraindications (Section 4.3) and warnings (Section 4.4), and these should be repeated during the use of Primolut Depot. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, and should also include cervical cytology. Pregnancy must be excluded in the appropriate indications.

Interaction with other medicaments and other forms of interaction

Drug interactions which result in an increased clearance of sex hormones can lead to decreased therapeutic efficacy. This has been established with many hepatic enzyme-inducing drugs (including phenytoin, barbiturates, primidone, carbamazepine, rifampicin, oxcarbazepine, St. Johns wort, and rifabutin); griseofulvin, is also suspected.

Sex steroids may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g. cyclosporin).

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

- Laboratory tests

The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Pregnancy and lactation

Pregnancy

Pregnancy should be ruled out unless Primolut Depot is being used for the treatment of habitual and threatened abortion.

Epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used sex steroids prior to pregnancy, nor a teratogenic effect when sex steroids were used inadvertently during early pregnancy.

A possible association between the administration of female sex hormones in early pregnancy and the occurrence of malformations has been the subject of discussions in recent years. According to the present state of scientific knowledge, the assumption that there may be a causal association can be regarded as unfounded. However, it must be clearly understood, that no drug - including sex hormones - can be claimed with absolute certainty to be free from teratogenic effects. This remaining uncertainty is the reason why, in certain indications, the exclusion of pregnancy is called for before the start of sex hormone therapy.

Lactation

Cyclical function is usually absent during lactation - particularly during short-lasting lactation. Since this is a physiological situation, there is no need to use Primolut Depot.

It is not known whether hydroxyprogesterone and its metabolites are excreted in human milk.

Effects on ability to drive or use machines

Not known.

Undesirable effects

The most serious undesirable effects associated with the use of progestogen only preparations are listed in Section 4.4 “Special warnings and special precautions for use“. In addition the

following undesirable effects have been reported in users of Primolut Depot although a causal relationship could not always be confirmed.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on reporting rates from postmarketing experience and literature.

System organ class	**Common (≥1/100)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**
Immune system disorders	Allergic skin reaction, e.g. Allergic rash, Allergic urticaria, Allergic edema			Anaphylactoid reaction
General disorders and administration site conditions	Injection site reaction, e.g. Injection site redness, Injection site swelling, Injection site pain			

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Respiratory, thoracic and mediastinal disorders

Experience has shown that the short-lasting reactions (Urge to cough, Paroxysmal cough, Respiratory distress) which occur in isolated cases during or immediately after the injection of oily solutions can be avoided by injecting the solution extremely slowly.

Overdose

On the basis of studies into the acute toxicity in experimental animals, the risk of adverse effects due to overdose appears low.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens

(ATC): G03D

Primolut Depot contains the progestogen hydroxyprogesterone caproate in oily solution. Hydroxyprogesterone caproate is an ester of the natural hydroxyprogesterone and exerts typical progestogenic effects in women, comparable to progesterone such as antigonadotrophic effects, secretory transformation of the endometrium and thickening of the cervical mucus. In opposite to the short-lasting progesterone, hydroxyprogesterone caproate has a progestogenic depot effect . Following intramuscular administration, maximum concentrations in the plasma are reached within 2-5 days. The thermogenic effect of the preparation is weak.

The administration of 250 mg hydroxyprogesterone caproate leads to secretory transformation of the endometrium; the effect lasts about 10 days if an estrogen is administered at the same time.

Primolut Depot does not inhibit the production of progesterone during the luteal phase and has no estrogenic, corticoid or androgenic effect. Moreover, it has no inhibitory effect on the placental production of hormones.

Pharmacokinetic properties

Absorption

Within 30 days after intramuscular administration, hydroxyprogesterone caproate was gradually and completely realeased from the depot. Hydroxyprogesterone caproate is completely bioavailable. The parent compound reached maximum concentrations in serum of 17 ± 6 ng/ml within 2-5 days after administration. Thereafter, the serum levels of hydroxyprogesterone caproate decreased slowly, and the compound was eliminated from the serum within 23 - 28 days post dose.

Distribution

There is no formation of secondary depots or deep compartments (e.g. fat) in the body.

Metabolism

Hydroxyprogesterone caproate is predominately metabolized as the complete steroid ester. Only small amounts of estradiol and its metabolites could be detected. The parent compound was practically not detectable in urine and feces indicating an almost complete metabolism of hydroxyprogesterone caproate in humans.

Elimination

Hydroxyprogesterone caproate and its metabolites were excreted with the bile and with the urine at a ratio of 8:2, respectively. An excretion half-life of about 6 days was calculated which characterizes the release of the drug from the depot.

Steady state conditions

During a once-weekly administration regimen, an accumulation of hydroxyprogesterone caproate and its metabolites of 100 % or more can be expected in the serum.

Preclinical safety data

Conventional animal studies aimed at clarifying repeated dose toxicity, carcinogenicity or mutagenicity have not been carried out with Primolut Depot or with its active ingredient hydroxyprogesterone caproate. Nor are they considered necessary for risk estimation in humans.
Hydroxyprogesterone caproate is an ester of hydroxyprogesterone which occurs physiologically in the intermediary metabolism. Therefore, if it is used in humans according to prescription, no symptoms of systemic intolerance or tumorigenic effects are to be expected. Due to the structure no mutagenic potential is to be expected.

However, it should be kept in mind that sex steroids might stimulate the growth of hormone-dependent tissues and tumors.

Reproductive toxicity studies gave no indication of a teratogenic potential of Primolut Depot nor of a damaging influence on the reproductive capacity of the following F1-generation.

Studies on the local tolerance of Primolut Depot did not indicate that hydroxyprogesterone caproate led to an increase of the irritative effect which was already caused by the solvent mixture alone.

PHARMACEUTICAL PARTICULARS

List of excipients

Benzyl benzoate

Castor oil for injection

Incompatibilities

In the absence of compatibility studies, this

medicinal product should not be mixed with other

medicinal products.

Presentation

Ampoules of 1 ml containing 250 mg

Special precautions for storage

Do not store above 30°C

Keep out of reach of children

Only on Prescription

DATE OF REVISION OF THE TEXT

20.03.2007

Manufacturer

Bayer Pharma AG

Physical address

13353 Berlin

Postal address

13342 Berlin

Germany