ProMax®

COMPOSITION:
Each ml contains:
Testosterone Propionate USP, Ph.Eur.100 mg
Testosterone Acetate 50 mg
Testosterone Phenylpropionate BP(Vet) 50 mg
Miglyol 840
Ethyl oleate
Benzyl benzoate
Benzyl alcohol

DESCRIPTION:
ProMax® is fast acting testosterone mix which is an oil based solution of 3 testosterone esters: propionate, acetate and phenylpropionate for intramuscular injection designed to reach peak testosterone serum levels within 24 hours of intramuscular administration and remain elevated for 2 to 4 days. ProMax® is suitable for the treatment of hypogonadism and other disorders related to androgen deficiency. ProMax® has both anabolic and androgenic effects. Testosterone supplementation has been demonstrated to increase strength and growth of new muscle tissue, frequently with increases in libido.

CLINICAL PHARMACOLOGY:
Testosterone and dihydrotestosterone are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution and have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. Hypogonadism is a risk factor for osteoporosis in men. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Esterification of testosterone at position 17 increases the lipid solubility of the testosterone molecule and prolongs the activity of the molecule by increasing its residence time. Following intramuscular administration in an oily vehicle, testosterone ester is slowly absorbed into the circulation and rapidly hydrolysed in plasma to testosterone.

In a study of healthy males, a single injection of 200 mg of Testosterone Cypionate increased mean serum testosterone concentrations sharply to 3 times the basal levels (approximately 1350 ng/dl) at 24 hours and declined gradually to basal levels (approximately 500 ng/dl) by day10.

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone. Testosterone is metabolized to DHT by steroid 5-alpha reductase located in the skin, liver, and the urogenital tract of the male. DHT binds with greater affinity to SHBG than does testosterone.

INDICATIONS AND USAGE:
Males: ProMax® is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:
A. Primary hypogonadism (congenital or acquired)--testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.
B. Hypogonadotropic hypogonadism (congenital or acquired)--idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.
If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.
C. ProMax® may be used to stimulate puberty in carefully selected males with clearly delayed puberty that is not secondary to a pathologic disorder, puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychologic support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be obtained every 6 months to assess the effect of treatment on the epiphyseal centers (See WARNINGS).
Females: ProMax® may be used secondarily in women with advancing in operable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or antiestrogen therapy.
This treatment has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor.
Judgement concerning androgen therapy should be made by an oncologist with expertise in this field.
ProMax® has been used for the management of postpartum breast pain and engorgement. (There is no satisfactory evidence that this drug prevents or suppresses lactation.)

CONTRAINDICATIONS:
ProMax® is contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking these drugs, she should be apprised of the potential hazard of the fetus.

WARNINGS:
In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case, the drug should be discontinued.
Prolonged use of high doses of androgens has been associated with the development of peliosis hepatitis and hepatic neoplasms, including hepatocellular carcinoma (See PRECAUTIONS-Carcinogenesis). Peliosis hepatic can be a life-threatening or fatal complication.
Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.
Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by addressing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child, the greater the risk of compromising final mature height.
Do not give ProMax® to elderly asthenic males who may react adversely to overstimulation by androgens.

LIVER CELL TUMORS ARE REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITH DRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS.
PELIOSIS HEPATIS, A CONDITION ARE ALSO REPORTED IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPERRANCE OF LESIONS.
BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS AND ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEIN AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEIN. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

PRECAUTIONS:
General Precautions: ProMax®, through its metabolic effects, stimulates the nervous, mental, and physical activities of a patient. Therefore, it should be used with caution in the presence of cardiovascular and renal diseases, especially in the elderly male.
Prolonged administration or excessive dosage may cause inhibition of testicular function. As the result, oligospermia may develop, and there may be a decrease in ejaculatory volume.
Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time mild virilism becomes evident is necessary to prevent irreversible virilization. Such virilization usually follows administration of androgens at high doses. A decision may be made by the patient and the physician concerning the degree of virilization that will be tolerated during treatment for breast carcinoma.
Anaphylactoid reactions, although rare, may occur, and treatment should be readily available.
Hypersensitivity reaction including rash and dermatitis have been reported.
Because androgens may alter serum cholesterol concentration, caution should be used when administering these drugs to patients with a history of myocardial infarction or coronary artery disease.
Patients on oral anticoagulant therapy require close monitoring especially when androgens are started or stopped.
Diabetics: androgens may alter the metabolism of oral hypoglycemic agents or may change insulin sensitivity in patients with diabetes mellitus which may require adjustment of dosage of insulin and other hypoglycemic drugs.
Information for the Patient
The physician should instruct patients to report any of the following side effects of androgens.
Adult or Adolescent Males: Too-frequent or persistent erections of the penis.
Women: Hoarseness, acne, changes in menstrual periods, or more hair on the face.
All Patients: Any nausea, vomiting, changes in skin color, or ankle swelling.
Any male adolescent patient receiving androgens for delayed puberty should have bone development checked every 6 months.
Carcinogenesis
Animal Data: testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human Data: There are rare reports of hepatocellular carcinoma in patients receiving longterm therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.
Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Usage in Pregnancy-Pregnancy Category X

Teratogenic effects (See CONTRAINDICATIONS).

Nursing Mothers

It is not known whether androgens are excreted in human milk, because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every 6 months by an x-ray of hand and wrist (See INDICATIONS AND USAGE and WARNINGS).

DRUG INTERACTIONS:

1. Oxyphenbutazone-Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbgutazone.
2. Insulin-In diabetic patients, the metabolic effects of androgens may decrease blood glucose and insulin requirements.

ADVERSE REACTIONS:

Endocrine and Urogenital

Female: The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman, androgens cause virilization of external genitalia of the female fetus.
Male: Gynecomastia, and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (See CLINICAL PHARMACOLOGY).
Skin and Appendages: Hirsutism, male pattern of baldness, and acne.
Fluid and Electrolyte Disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.
Patients with osteolytic neoplastic lesions who are bedfast or only semiambulatory may develop nephrocalcinosis when given either estrogens or androgens.
Gastrointestinal: Nausea and, rarely, hepatocellular neoplasms and peliosis hepatic (See WARNINGS).
Hematologic: Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.
Nervous System: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
Metabolic: Increased serum cholesterol.
Miscellaneous: Inflammation and pain at the site of intramuscular injection, and , rarely, anaphylactoid reactions.

OVERDOSAGE:

There have been no reports of acute overdosage with the androgens.

PATIENT MONITORING:

Serum Cholesterol, HDL, LDL, TG. Hemoglobin and Hematocrit, Hepatic function tests – AST/ALT Prostatic specific antigen – PSA, Testosterone: total, free, and bioavailable. Dihydrotestosterone & Estradiol Male patients over 40 should undergo a digital rectal examination and evaluate PSA prior to androgen use. Periodic evaluations of the prostate should continue while on androgen therapy, especially in patients with difficulty in urination or with changes in voiding habits.

DOSAGE AND ADMINISTRATION:

ProMax® is administered by intramuscular injection. It must not be given intravenously. Intramuscular injections should be given deep in the gluteal muscle.
The suggested dosage varies, depending on the age, sex, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions, and maintenance doses should be the minimum that produce adequate effect. This preparation is absorbed relatively slowly, and frequent injection may cause overdosage.
Replacement therapy in androgen-deficient males should be in the range of 25-50 mg 2 or 3 times a week.
Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower dosages initially, gradually increasing the dose as puberty progresses. With or without a decrease to maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes, and lower dosages can be used for maintenance after puberty. The chronologic and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dosage.
Dosages used in delayed puberty generally are in the lower ranges and are for a limited duration, for example, 4 to 6 months.
Carcinoma of the Breast: In inoperable carcinoma of the breast, temporary palliation may be obtained in some cases by therapy with androgens. A dosage of 50-100 mg of ProMax® administered intramuscularly 3 times weekly is recommended. If a response to androgen therapy is going to occur, it will be apparent within 3 months after initiation of therapy. When the disease again becomes progressive, therapy should be stopped and the patient observed for another period of improvement, known as rebound regression. The above high dosage is likely to have masculinizing effects, particularly in young women. There may be a disturbing increase in libido, for which sedation may be helpful. It should be remembered that acceleration of tumor growth may be encountered occasionally during androgen therapy, in which case immediate cessation of the hormone is indicated. In some of these cases, the use of estrogen at this point causes regression.
Postpartum Engorgement of the Breasts: A dosage of 25 to 50 mg of ProMax® daily for 3 to 4 days, starting at the time of delivery, should be adequate in most cases.

HOW SUPPLIED – ProMax® Injection, Solution- Intramuscular-200 mg/ml is supplied in multiple dose 10 ml vial with dark pink color flip cap.

For shelf-life please refer to the imprint on the pack.

Keep out of reach of children.

Should be at controlled room temperatures 15-30°C (59-86°F)

Do not freeze

This drug should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Warming and shaking the vial should redissolve any crystals that may have formed during storage at temperatures lower than recommended.

Protect from sun light

This drug has not been shown to be safe and effective for the enhancement of athletic performance!

Manufactured and Distributed by: LA Pharma S.r.l.

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