BTG PHARMACEUTICALS

OXANDRIN®

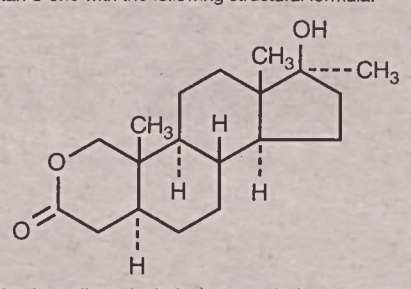
(oxandrolone tablets, USP)

C III

Revised: Aug. 30, 1996

DESCRIPTION

Oxandrin® oral tablets contain 2.5 mg of the anabolic steroid oxandrolone. Oxandrolone is 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one with the following structural formula:



Inactive ingredients include cornstarch, lactose, magnesium stearate, and hydroxypropyl methylcellulose.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

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

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

INDICATIONS AND USAGE

Oxandrin is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (See **DOSAGE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

1. Known or suspected carcinoma of the prostate or the male breast.
2. Carcinoma of the breast in females with hypercalcemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
3. Pregnancy, because of possible masculinization of the fetus. Oxandrin has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
4. Nephrosis, the nephrotic phase of nephritis.
5. Hypercalcemia.

WARNINGS

PELIOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING 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 DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL 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. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (See **PRECAUTIONS: Laboratory tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

General:
Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for patients:
The physician should instruct patients to report any of the following side effects of androgens:

Males: Too frequent or persistent erections of the penis, appearance or aggravation of acne.
Females: Hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients: Nausea, vomiting, changes in skin color, or ankle swelling.

Laboratory tests:
Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy (See **WARNINGS**).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Serum lipids and high-density lipoprotein cholesterol determinations should be done periodically as androgenic anabolic steroids have been reported to increase low-density lipoproteins. Serum cholesterol levels may increase during therapy. Therefore, caution is required when administering these agents to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug interactions

Anticoagulants:
Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Oral hypoglycemic agents:
Oxandrolone may inhibit the metabolism of oral hypoglycemic agents.

Adrenal steroids or ACTH:
In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory test interactions:
Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, mutagenesis, impairment of fertility

Animal data:
Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human data:
Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (See **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy:
Teratogenic effects—Pregnancy Category X (See **CONTRAINDICATIONS**).

Nursing mothers:
It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, 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:
Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (See **WARNINGS**).

ADVERSE REACTIONS

The following adverse reactions have been associated with use of anabolic steroids:

Hepatic: Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis with long-term therapy (See **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulfophthalein (BSP) retention, and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alkaline phosphatase.

In *males:*
Prepubertal: Phallic enlargement and increased frequency or persistence of erections.
Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.

In *females:*
Clitoral enlargement, menstrual irregularities.

CNS: Habituation, excitation, insomnia, depression, and changes in libido.

Hematologic: Bleeding in patients on concomitant anticoagulant therapy.

Breast: Gynecomastia.

Larynx: Deepening of the voice in females.

Hair: Hirsutism and male pattern baldness in females.

Skin: Acne (especially in females and prepubertal males).

Skeletal: Premature closure of epiphyses in children (See **PRECAUTIONS: Pediatric use**).

Fluid and electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).

Metabolic/Endocrine: Decreased glucose tolerance (See **PRECAUTIONS: Laboratory tests**), increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD_{50} of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSAGE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrin (oxandrolone) will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults: The *usual adult* dosage of Oxandrin is one 2.5-mg tablet 2 to 4 times daily. However, the response of individuals to anabolic steroids varies, and a daily dosage of as little as 2.5 mg or as much as 20 mg may be required to achieve the desired response. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.

Children: For children the total daily dosage of Oxandrin is ≤0.1 mg per kilogram body weight or ≤0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

HOW SUPPLIED

Oxandrin 2.5-mg tablets are oval, white, and scored with BTG on one side and "11" on each side of the scoreline on the other side; bottles of 100 (NDC 54396-111-11).
Caution: Federal law prohibits dispensing without prescription.

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BTG PHARMACEUTICALS

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