CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 085635Orig1s011

Name: Depo-Testosterone (Testosterone Cypionate Injection USP)
100 mg/mL and 200 mg/mL

Sponsor: The Upjohn Company

Approval Date: July 11, 1991

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s011

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APPLICATION NUMBER:

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APPROVAL LETTER

JUL 11 1991

ANDA 85-635/S-011

The Upjohn Company
Attention: J. R. Azzenzo, Ph.D.
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Sir:

Reference is made to your supplemental new drug application dated April 17, 1991, submitted pursuant to Section 314.70(c) (Special Supplement-Changes Being Effected) of the Regulations, regarding your abbreviated new drug application for Depo®-Testosterone (Testosterone Cypionate Injection USP) 100 mg/mL and 200 mg/mL.

The supplemental application provides for revised container labels (100 mg/mL -10 mL, 200 mg/mL - 1 mL and 10 mL), carton and package insert labeling reflecting the addition of the controlled substance symbol. The package insert also reflects the addition of a DRUG ABUSE AND DEPENDENCE section and the addition of a paragraph in the WARNINGS section.

We have completed the review of this supplemental application and it is approved. Our letter of July 25, 1979, detailed the conditions relating to the approval of this abbreviated application.

We note the insert no longer references the 1 mL package size for the 100 mg/mL product and that a container label was not submitted for this package size. Was this intentional? If so, we believe you should have informed us of this in your cover letter.

The material submitted is being retained in our files.

Sincerely yours,

Roger L. Williams, M.D. /RA 7-10-91
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc;
HFD-638
HFD-600
HFC-130/JAllen
KShah/YMille
kt (hab) 86635S11.L
APPROVAL

7/10/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s011

LABELING

Upjohn

Depo®-Testosterone

brand of testosterone cypionate sterile solution
(testosterone cypionate injection, USP)

C III

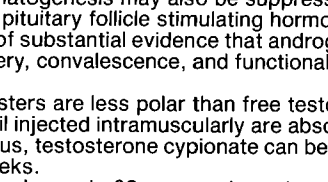
DESCRIPTION

DEPO-Testosterone Sterile Solution, for intramuscular injection, contains testosterone cypionate which is the oil-soluble 17 (beta)-cyclopentylpropionate ester of the androgenic hormone testosterone.

Testosterone cypionate is a white or creamy white crystalline powder, odorless or nearly so and stable in air. It is insoluble in water, freely soluble in alcohol, chloroform, dioxane, ether, and soluble in vegetable oils.

The chemical name for testosterone cypionate is androst-4-en-3-one,17-(3-cyclopentyl-1-oxopropoxy)-, (17β)-. Its molecular formula is $C_{27}H_{40}O_3$, and the molecular weight 412.61.

The structural formula is represented below:



DEPO-Testosterone is available in two strengths, 100 mg/mL and 200 mg/mL testosterone cypionate.

Each mL of the **100 mg/mL** solution contains:

Testosterone cypionate	100 mg
Benzyl benzoate	0.1 mL
Cottonseed oil	736 mg
Benzyl alcohol (as preservative)	9.45 mg

Each mL of the **200 mg/mL** solution contains:

Testosterone cypionate	200 mg
Benzyl benzoate	0.2 mL
Cottonseed oil	560 mg
Benzyl alcohol (as preservative)	9.45 mg

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, and phosphorous, and decreased urinary excretion of calcium. 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.

Androgens are responsible for the growth spurt of adolescence and for eventual termination of linear growth, brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate production of red blood cells by enhancing production of erythropoietic stimulation factor.

During exogenous administration of androgens, endogenous testosterone release is 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).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

Pharmacokinetics

Testosterone esters are less polar than free testosterone. Testosterone esters in oil injected intramuscularly are absorbed slowly from the lipid phase; thus, testosterone cypionate can be given at intervals of two to four weeks.

Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about 2 percent is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90 percent of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6 percent of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways.

The half-life of testosterone cypionate when injected intramuscularly is approximately eight days.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

DEPO-Testosterone Sterile Solution is indicated for replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone.

1. Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.
2. Hypogonadotropic hypogonadism (congenital or acquired)-idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

CONTRAINDICATIONS

1. Known hypersensitivity to the drug
2. Males with carcinoma of the breast
3. Males with known or suspected carcinoma of the prostate gland
4. Women who are or who may become pregnant
5. Patients with serious cardiac, hepatic or renal disease

WARNINGS

Hypercalcemia may occur in immobilized patients. If this occurs, the drug should be discontinued.

Prolonged use of high doses of androgens (principally the 17-α alkyl-androgens) has been associated with development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis —all potentially life-threatening complications.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease.

Gynecomastia may develop and occasionally persists in patients being treated for hypogonadism.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing 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.

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

PRECAUTIONS

General: Patients with benign prostatic hypertrophy may develop acute urethral obstruction. Priapism or excessive sexual stimulation may develop. Oligospermia may occur after prolonged administration or excessive dosage. If any of these effects appear, the androgen should be stopped and if restarted, a lower dosage should be utilized.

Testosterone cypionate should not be used interchangeably with testosterone propionate because of differences in duration of action.

Testosterone cypionate *is not* for intravenous use.

Information for patients: Patients should be instructed to report any of the following: nausea, vomiting, changes in skin color, ankle swelling, too frequent or persistent erections of the penis.

Laboratory tests: Hemoglobin and hematocrit levels (to detect polycythemia) should be checked periodically in patients receiving long-term androgen administration.

Serum cholesterol may increase during androgen therapy.

Drug interactions: Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Drug/Laboratory test Interferences: Androgens 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, however, and there is no clinical evidence of thyroid dysfunction.

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 long-term 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 of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

Pregnancy: Teratogenic Effects. Pregancy Category X. (See CONTRAINDICATIONS).

Nursing mothers: DEPO-Testosterone is not recommended for use in nursing mothers.

Pediatric use: DEPO-Testosterone is not recommended for use in children.

ADVERSE REACTIONS

The following adverse reactions in the male have occurred with some androgens:

Endocrine and urogenital: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages.

Skin and appendages: Hirsutism, male pattern of baldness, seborrhea, and acne.

Fluid and electrolyte disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular neoplasms and peliosis hepatis (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.

Allergic: Hypersensitivity, including skin manifestations and anaphylactoid reactions.

Miscellaneous: Inflammation and pain at the site of intramuscular injection.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Testosterone is a controlled substance under the Anabolic Steroids Control Act, and DEPO-Testosterone Sterile Solution has been assigned to Schedule III.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

DEPO-Testosterone Sterile Solution is for intramuscular use only.

It should not be given intravenously. Intramuscular injections should be given deep in the gluteal muscle.

The suggested dosage for DEPO-Testosterone Sterile Solution 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.

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 chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

For replacement in the hypogonadal male, 50-400 mg should be administered every two to four weeks.

Parenteral drug products 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.

HOW SUPPLIED

DEPO-Testosterone Sterile Solution is available as follows:

100 mg/mL	
10 mL vials	NDC 0009-0347-02
200 mg/mL	
1 mL vials	NDC 0009-0417-01
10 mL vials	NDC 0009-0417-02

Vials should be stored at controlled room temperature 15°-30° C (59°-86° F) and protected from light.

Caution: Federal law prohibits dispensing without prescription.

The Upjohn Company • Kalamazoo, Michigan 49001, USA

Revised March 1991 811 020 007α

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JUL 1 1 1991

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

THE UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001-0199

U.S. Pharmaceutical Regulatory Affairs
J. R. Assenzo, Ph.D., Executive Director
THE UPJOHN COMPANY
(616) 329-8216

PI and Labels + carton labeling container - 1 mL + 10 mL (200 mg/mL - 10 mL) 100 mg/mL - 10 mL) satisfactory 5/30/91

NDA NO.________ REF NO. S17/011

NDA SUPPL FOR

April 17, 1991

RECEIVED

APR 19 1991

GENERIC DRUGS

Division of Metabolism and Endocrine
Drug Products, HFD-510
Document Control #14B-03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

Re: ANDA ~~#86-635~~ 85-635
DEPO®-TESTOSTERONE
Sterile Solution
(testosterone cypionate)

Dear Sir/Madam:

Under the provisions of 21 CFR §314.70(c)(2)(ii) we are submitting a Special Supplement to add a Drug Abuse and Dependence section to the package insert for DEPO®-TESTOSTERONE Sterile Solution. This action is being taken to comply with the following: the Anabolic Steroids Control Act of 1990; a Drug Enforcement Administration final rule that implements this Act and was published in the February 13, 1991 Federal Register (Volume 56, No. 30, pages 5753-5754, copy attached); and 21 CFR §201.57(h)(1).

The new section reads:

"DRUG ABUSE AND DEPENDENCE

> Controlled substance class: Testosterone is a controlled substance under the Anabolic Steroids Control Act, and DEPO®-TESTOSTERONE Sterile Solution has been assigned to Schedule III."

22 Apr 91
P. Mills

In addition, we have also revised the vial labels and carton copy to include the Controlled Substance symbol for Schedule III drug products as required by 21 CFR §1302. The symbol also appears on the revised package insert.

Twelve copies of the following final printed labeling is attached:

Package insert (copy code 811 020 007α)

100 mg/mL
10 mL vial
vial label (copy code 811 026 104α)
carton copy (copy code 811 016 105α)

200 mg/mL
1 mL vial
vial label (copy code 811 025 203α)
carton copy (copy code 811 031 204α)

10 mL vial
vial label (copy code 811 036 104α)
carton copy (copy code 811 040 106α)

We plan to implement the revised labeling effective May 17, 1991. If you have any questions, please call Ronald Leong, M.D. at (616) 329-5628.

Sincerely,

THE UPJOHN COMPANY

Ronald W. Leong, MD for

J. R. Assenzo, Ph.D.
Executive Director
U.S. Pharmaceutical Regulatory Affairs

JRA/RWL/bl
Attachment

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

U.S. Pharmaceutical Regulatory Affairs
J. R. Assenzo, Ph.D., Executive Director
THE UPJOHN COMPANY
(616) 329-8216

July 24, 1991

Division of Generic Drugs, HFD-230
Center for Drug Evaluation and Research
Document Control Room #17-46
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: ANDA 85-635/S-011
DEPO®-Testosterone Sterile Solution
(testosterone cypionate injection, USP)

Dear Sir/Madam:

Reference is made to your letter of July 16, 1991 concerning the above, in which you mention the absence of the 1 mL package size for the 100 mg/mL product.

This package size was discontinued February 9, 1990.

If you have questions, please contact Peggy English at (616) 329-5286.

Sincerely,

THE UPJOHN COMPANY

Peggy English for

J. R. Assenzo, Ph.D.
Executive Director
U.S. Pharmaceutical Regulatory Affairs

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