CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 085635Orig1s013

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

Sponsor: Pharmacia & Upjohn Company

Approval Date: April 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s013

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Statistical Review(s)	
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Other Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s013

APPROVAL LETTER

ANDA 85-635/S-013

Pharmacia & Upjohn Company
Attention: Dora W. Cohen
7000 Portage Road
Kalamazoo, MI 49001

APR 30 1997

Dear Madam:

This is in reference to your supplemental new drug application dated September 6, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Depo®-Testosterone (Testosterone Cypionate Injection, USP) 100 mg/mL and 200 mg/mL.

Reference is also made to your amendment dated February 14, 1997.

The supplemental application provides for revisions to the PRECAUTIONS, Pediatric use subsection of the package insert labeling to be in accord with the labeling requirements in 21 CFR 201.57(f)(9).

We have completed the review of this supplemental application and it is approved. However, at the time of next printing or within 180 days, whichever is sooner, revise your insert as follows:

> The established name must appear in conjunction with the proprietary name at least once in the running text of the insert. We refer you to 21 CFR 201.10(g). Please revise your labeling accordingly.

Prepare and submit final printed labeling as a supplement to this approved application.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

John Good for 4-30-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: cc: ANDA 85-635/S-013
Division File
HFD-92/with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
njg/4/22/97/X:\NEW\FIRMSNZ\PHARMACI\LTRS&REV\85635S13.APL
APPROVAL LETTER - SINGLE SUPPLEMENT

Endorsements:
HFD-613/CHolquist C. Holquist 4-22-97
HFD-613/Avezza A. Uezza 4-22-97
HFD-613/JGrace

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635s013

OTHER ACTION LETTER

ANDA 85-635/S-013

Pharmacia & Upjohn Company
Attention: Dora W. Cohen
7000 Portage Road
Kalamazoo, MI 49001

DEC 2 1996

Dear Madam:

This is in reference to your supplemental new drug application dated September 6, 1996, submitted pursuant to 21 CFR 314.70 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 revisions to the PRECAUTIONS, Pediatric use subsection of the package insert labeling to be in accord with the labeling requirements in 21 CFR 201.57(f)(9).

We have completed the review of this supplemental application and it is approvable. However, before the supplemental application may be approved, it is necessary that you revise the following:

INSERT

The requirements of 21 CFR 201.10(g) must be met. The established name must appear in certain sections in association with the proprietary name. Please revise your labeling accordingly.

In addition, all submissions and other correspondence intended to be a part of an ANDA or an AADA, whether sent by U.S. Mail or by courier service or by a parcel service, should be addressed as follows:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Prepare and submit final printed labeling as an amendment to this supplemental application.

The changes provided for in this supplemental application may not be initiated until you have been notified in writing that the supplemental application is approved.

Sincerely yours,

Robert Lumpkin for 12/2/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 85-635/S-013
Division File
HFD-600/Reading File
HFD-613/CHolquist/JGrace (no cc:)
njg/11/25/96/x:\new\firmsnz\upjohn\ltrs&rev\85635s13.nal
Approvable Letter - Single Supplement

awg 11/26/96
Catalogued 11/25/96
11/27/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s013

LABELING

Depo®-Testosterone

sterile solution

Pharmacia &Upjohn

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

APR 30 1997

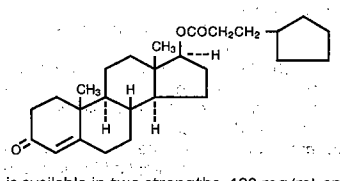
DESCRIPTION

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.

Depo®-Testosterone
testosterone cypionate
sterile solution
(testosterone cypionate
injection, USP)

0811020110

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.

Depo-Testosterone

brand of testosterone cypionate sterile solution

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 discontinued or, 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

(continued below)

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. Pregnancy Category X. (See CONTRAINDICATIONS.)

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

Pediatric use: Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

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 Solutions 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 20° to 25° C (68° to 77° F) [see USP]. Protect from light.

Caution: Federal law prohibits dispensing without prescription.

Pharmacia & Upjohn Company • Kalamazoo, Michigan 49001, USA

Revised January 1997

811 020 110α
691272

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 085635Orig1s013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Pharmacia & Upjohn

NDA NO.__________ REF. NO. SL013

NDA SUPPL FOR Labeling Rev

Draft

Dora W. Cohen
Regulatory Manager
U.S. Market Company
Regulatory Affairs
Mailstop 0632-298-113

Phone: 833-8334
Fax: (616) 833-8237

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 13 1996
CDR

Approvable
Need supplement letter
11/14/96

September 6, 1996

Division of Reproductive & Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Document Control Room 17b-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 85-635
DEPO®-Testosterone
(testosterone cypionate sterile solution)

Dear Sir/Madam:

We are supplementing our New Drug Application for the above to request approval for a revised package insert. The revised insert is provided in Attachment 1.

The revision affects the Pediatric Use subsection of the PRECAUTIONS section and consists of modifying that subsection slightly. The previous statement: "DEPO-Testosterone is not recommended for use in children" has been changed to "Safety and effectiveness in pediatric patients below the age of 12 years have not been established." This change is being made in consideration of the labeling requirements as stated in 21 CFR §201.57(f)(9). The revised statement is consistent with the indications for the product.

Please contact Dora W. Cohen at (616) 833-8334 if you have any questions about this labeling and send any correspondence to mailstop 0632-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Dora W Cohen

Dora W. Cohen
Regulatory Manager
U.S. Market Company-Regulatory Affairs

DWC:rlc

Attachments

RECEIVED
SEP 23 1996
GENERIC DRUGS

REC'D
SEP 18 1996
HFD-580

Pharmacia&Upjohn

Dora W. Cohen
Regulatory Manager
U.S. Market Company-Regulatory Affairs
Mailstop 0632-298-113

Phone: 833-8334
Fax: (616) 833-8237

Approvable letter
Didn't revise labeling as requested in 12/2/96 letter
C. Hulquist
4/10/97

February 14, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA SUPPL AMENDMENT
SL013/AL

Re: NDA 85-635/S-013
DEPO®-Testosterone
(testosterone cypionate sterile solution)

FINAL PRINTED LABELING

Dear Sir/Madam:

As requested in the Agency's letter of December 2, 1996, we are submitting 20 copies of the final printed labeling (copy code 811 020 110) as an amendment for the above mentioned product. We understand that this labeling can not be implemented until written approval is received from the Agency.

Please contact Dora W. Cohen at (616) 833-8334 if you have any questions about this labeling. Please send any correspondence to mailstop 0632-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Dora W. Cohen
Regulatory Manager
U.S. Market Company-Regulatory Affairs

DWC:aed

Attachments

RECEIVED
FEB 18 1997
GENERIC DRUGS

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000