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
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APPLICATION NUMBER:
ANDA 085635Orig1s011

APPROVAL LETTER
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.  
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
APPLICATION NUMBER:
ANDA 085635Orig1s011

LABELING
Depo-Testosterone
brand of testosterone cypionate sterile solution
(testosterone cypionate injection, USP)

DESCRIPTION
Depo-Testosterone Sterile Solution, for intramuscular injection, contains testosterone cypionate which is the oil solution of testosterone cypionate/propionate ester of the androgenic testosterone. Testosterone cypionate is a white or colorless, odorless, tasteless powder, colorless or nearly so and stable in air. It is insoluble in water, freely soluble in chloroform, benzyl alcohol, diacetyl and vegetable oils.

The chemical name for testosterone cypionate is androst-4-en-3-one, 17β-cyclopentyl-1-oxopropionylate. [199]. Its molecular formula is C23H32O3; molecular weight is 336.52 Cm.

The structural formula is represented below:

Depo-Testosterone is available in two strengths, 100 mg and 200 mg per milliliter of testosterone cypionate.

Each mL of the 100 mg solution contains:
Testosterone cypionate 100 mg
Benzyl alcohol 0.1 mL
Cottonseed oil 0.9 mL
Benzyl alcohol (preservative) 9.6 mg

Each mL of the 200 mg solution contains:
Testosterone cypionate 200 mg
Benzyl alcohol 0.2 mL
Cottonseed oil 1.8 mL
Benzyl alcohol (preservative) 19.2 mg

CLINICAL PHARMACOLOGY
Effective androgens are responsible for normal growth and development in male and female organisms. In order for maintenance of reproductive function, libido, and secondary sex characteristics to be present in both sexes, adequate androgen levels must be maintained. Adverse effects of androgens include growth stimulation of the prostate, seminal vesicles, and accessory glands; development of muscle mass and and secondary sex characteristics (vocal, sexual, and axillary hair; larger body size; vocal cord thickening; and alterations in libido) and skin and hair coloration. In addition, there is also the cause of retention of sodium, potassium, phosphorus, and water. Both acute and chronic administration of androgens have been reported to increase protein anabolism and decrease protein catabolism. Hyperaemia of the skin is commonly improved only with the increased flow of blood and increased 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 epiphyses of long bones. In children, androgens accelerate linear growth rates, but may cause disproportionate advancement in bone maturity. Over long periods of time in fusion of the epiphyses the growth centers and termination of the growth process. Androgens have been reported to stimulate production of red blood cells by enhancing production of erythropoietin stimulation factor.

During exogenous administration of androgens, endogenous testosterone synthesis is suppressed (77.81). At large doses of exogenous androgens, seminal plasma volume may also be suppressed. Androgen excess may lead to infertility in men and is associated with carcinoma of the prostate in men.

There is a lack of substantial evidence that androgens are effective in fractures, myopathy, anemia, and functional uterine bleeding. Pharmacokinetics
Testosterone esters in oil are absorbed incompletely and slowly from the injection site. Testosterone cypionate can be given at intervals of two to four weeks. Testosterone cypionate is 98 percent bound to a specific testosterone-estradiol-binding globulin, and about 3 percent is free. Generally, the extent of testosterone bioavailability in humans is determined by the plasma concentration of testosterone and the free testosterone concentration will determine its half-life.

About 90 percent of a dose of testosterone is excreted in the urine as glucuronide and sulfuric acid conjugates of testosterone and its metabolites; about 10 percent of a dose is excreted in the feces. Testosterone is metabolized to testosterone and androstenedione in two different pathways.

The half-life of testosterone cypionate when injected intramuscularly is approximately eight days. In many tissues, testosterone appears to depend on reoxidation to dihydrotestosterone, which binds to cytosol receptor protein. The cytosol-receptor complex is transported to the nucleus, 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 testicular, orchitis, varicocele, metastatic tumors; or orchidectomy.
2. Hypogonadotropic hypogonadism (congenital or acquired)-ido- diagnosis of chronic renal failure, 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 who have known or suspected carcinoma of the prostate gland
4. Women who are or may become pregnant
5. Patients with serious cardiac, hepatic or renal disease

WARNINGS
Hypersensitivity may occur in immunosuppressed patients. If this occurs, the drug should be discontinued.

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

Genetic 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.

Ectopic, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac 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 patients with a previous history of depression. 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 extent of compromising final maturation height.

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

PRECAUTIONS
General: Patients with benign prostatic hypertrophy may develop acute urinary obstruction. Priapism or excessive sexual stimulation may develop. Oligospermia may preclude the use of Depo-Testosterone for intramuscular use. 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 must be instructed to report any of the following: nausea, vomiting, changes in skin color, allergic swelling, too frequent or persistent erections or priapism.

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

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

Concurrent administration of antihypertensive and androgenic substances such as clomipramine can lead to hypotension.

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 proteins, resulting in increased total T4 serum levels and increased resin uptake of T3 and T4. 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 included carcinogenic chromosomal tumors in female mice and chemically-induced carcinomas of the liver in rats.

Human data: Studies of the effect of chronic administration of estrogenic and androgenic substances on the development of hepatic cell carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drug resulted in regression of the tumors in most cases.

Senescence of 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 and PRECAUTIONS).

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

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

Induction and unresponsiveness: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high doses.

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

Integument: Change in skin color, anhidrosis.

Genitourinary: Enuresis, nocturia, penile edema.

Musculocutaneous: Atrophy of fat and muscle, reduced gynecoid distribution, increase in body weight.

Blood: Increased protein anabolism and decreased protein catabolism.

Nervous system: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Allergic: Anaphylactic shock, including skin manifestations and anaphylactoid reactions.

Miscellaneous: Amenorrhea and amenorrhea-like pain at the site of intramuscular injections.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Testosterone is a controlled substance under the Federal Controlled Substances Act and DEPO-Testosterone Sterile Solution has been scheduled to Schedule III.

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

DOSEAGE AND ADMINISTRATION
DEPO-Testosterone Sterile Solution is for intramuscular use only. It should not be used for injection into the sheath and the dose should be given deep in the gluteal muscles.

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 produce 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 stimulate pubertal changes and lower dosages can be used for maintenance after puberty. The clinical androgenological and skeletal age must be considered 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 used specifically for particular matter and identification prior to administration, whenever solution and container are used for the first time. If the solution should become cloudy, refrigerate it until the crystals have dissolved. Thereafter, the solution should be used if it is clear within the temperature range of 58-59°F (16°C-16°C) and protected from light.

Caution: Federal law prohibits dispensing without prescription.

The Upjohn Company • Kalamazoo, Michigan 49001-0000

Revised March 1991

811 020 007a.
APPLICATION NUMBER:
ANDA 085635Orig1s011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
DIVISION OF METABOLISM AND ENDOCRINE
Drug Products, HFD-510
Document Control #44B-03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

April 17, 1991

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)(l).

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."
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

[Signature]

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

JRA/RWL/bl
Attachment
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

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