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
## CONTENTS

<table>
<thead>
<tr>
<th>Reviews / Information Included in this Review</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Other Action Letter(s)</td>
<td>X</td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Labeling Review(s)</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Other Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative &amp; Correspondence Documents</td>
<td>X</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
ANDA 085635Orig1s013

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

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,

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-92/with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
njg/4/22/97/X:\NEW\FIRMSNZ\PHARMACILTRS&REV\85635S13.APL
APPROVAL LETTER - SINGLE SUPPLEMENT

Endorsements:
HFD-613/CHolquist 1-22-97
HFD-613/Avezza 1-22-97
HFD-613/JGrace 1-22-97
APPLICATION NUMBER:
ANDA 085635s013

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

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,

[Signature]

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\1trs&rev\85635s13.nal
Approuvable Letter - Single Supplement
DESCRIPTION

Depo-Testosterone Sterile Solution, for Intramuscular Injection, contains testosterone propionate which is the oil solution of 17β-cyano-17α-propionyl testosterone.

Testosterone propionate is a white or creamish white crystalline powder, colorless or nearly so, and stable in air. It is insoluble in water, freely soluble in alcohol, chloroform, xylene, ether, and in vegetable oils. The chemical name for testosterone propionate is androst-4-en-3-one-17β-(3-cyano-1-propionyl)propionate -17β. Its molecular formula is C23H32N2O5, and the molecular weight is 402.5.

The structural formula is represented below:

Depo-Testosterone is available in two strengths, 100 mg/ml and 200 mg/ml testosterone propionate.

CLINICAL PHARMACOLOGY

Androgenic and anabolic actions 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, breast atrophy, larynx enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. In this class also cause retention of nitrogen, sodium, potassium, and phosphorous, and decrease hydrochloric acid excretion. These effects are associated with an increase in red cell mass, increase bone density and decrease protein catabolism. Nitrogen balance is improved only when there is a sufficient intake of caloric and protein.

Androgens are responsible for the growth spurt of adolescence and for eventual termination of linear growth. Growth of the pubic hair begins at about the same time of the adolescent growth spurt in children. Exogenous androgenic accelerates linear growth rates, but may cause disproportionate advancement in bone maturation, i.e., over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens may be used to stimulate production of red blood cells in anemic conditions, particularly in anemia of chronic disease; to increase endogenous production of protein in cases of malnutrition and debilitation; and to stimulate spermatogenesis in the presence of pituitary deficiencies.

There is a lack of substantial evidence that androgens are effective in fractures, burns, convalescence, and functional urinary incontinence.

PHARMACOKINETICS

Testosterone esters are less potent than free testosterone. Testosterone esters in oil injected intramuscularly are absorbed slowly from the lipoidal phase; thus, testosterone cypionate can be given as infrequently as two to four weeks.

Testosterone propionate in a 1:1 per cent oil solution is a lipoidal substance, and about 1 percent is in the blood within the first hour after injection. The concentration in the blood decreases rapidly, with about 3 percent free and 22 percent in the form of biologically inactive bound or protein-bound forms. The free testosterone concentration will determine its half-life.

About 96 percent of a dose of testosterone is excreted in the urine as glucuronides and sulfates, and conjugates of testosterone and its metabolites. About 4 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 4-androstene-3,17-dione derivatives through two different pathways.

The half-life of testosterone propionate when injected intramuscularly is approximately 2 days.

In many tissues, the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to intracellular receptors. The staniol-reduction enzyme is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

Enlarged Prostate: Testosterone cypionate is indicated for replacement therapy in the male in conditions associated with symptoms of deficiency, or absence of endogenous testosterone.

1. Primary hypogonadism (benign or acquired) or testicular failure due to cryptorchidism, bilateral orchidectomy, orchiectomy, andchioma, or orchitis.

2. Hypogonadal microhypogonadism or acquired idiopathic gonadotropin deficiency or Leydig cell deficiency, or pituitary hypogonadal men from trauma, irradiation, or radiation.

CONTRAINDICATIONS

1. Known hypersensitivity to the drug.

2. Male with carcinoma of the breast.

3. Male with 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

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

Increased risk of death of androgens is particularly the 17α-alcohol-17β-propionate has been associated with development of hepatic neoplasms, hepatic failure, carcinoma, and peptic ulcers - all potentially life-threatening complications.

Carcinogenic potential of androgens may be of an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

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

Concomitant use may develop in a variety of patients in persons being treated for hypogonadal conditions. This product contains benzoate alcohol. Benzoic alcohol has been reported to be associated with a rare, "causative function" in premature infants.

Patients with a history of heart failure, or who have been warned of possible complications with weight changes care should be taken to avoid fluid retention. The effect on bone-muscularization should be monitored by assessing change in the body weight of any weight or other significant advances in bone maturation without producing compensatory gain in linear growth. The 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 purposes.
testosterone into some strains of female mice increases their susceptibility to hyperplasia. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas in the liver in rats.

Human data. There are few reports of hepatic tumors in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drug did not result in regression of the tumors in all cases. Persistent or persistent tumors treated with androgens may be at an increased risk of developing malignant tumors. Progesterone, a common constituent of oral contraceptives, has a carcinogenic effect in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone in mice and rats increases susceptibility to hepatic hyperplasia.

PRECAUTIONS

General. Testosterone treatment causes an increase in the amount of fat in the body. Testosterone also increases the amount of water in the body. Testosterone treatment is not recommended for use in men with prostate or breast cancer.

Drug/Laboratory test Interferences: Androgens may decrease levels of serum calcium, and may increase levels of serum phosphates.

ADVERSE REACTIONS

The following adverse reactions in the male have occurred with some androgens, finasteride and nandrolone. Gastrointestinal: Nausea, vomiting, and diarrhea. Cardiovascular: Hypertension, edema, and flushing. Dermatologic: Acne, loss of hair, hypertrichosis, and seborrhea. Neuropsychiatric: Headache, dizziness, and depression.

OVERDOSAGE

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

Depo-Testosterone Sterile Solution is administered by intramuscular injection. The dose should be based on the needs of the individual patient.

HOW SUPPLIED

Depo-Testosterone Sterile Solution is available as follows:

100 mg per 1 ml:

10 ml vials: 1000-000-0047-00
200 mg per 1 ml:

10 ml vials: 1000-000-0047-01

Depo-Testosterone Sterile Solution is non-pyrogenic. Protect from light.

Caution: Federal law prohibits dispensing without prescription.

Pharmaceutical Supply Company • 511-610-1415

Revised January 1997

B160-2171
Pharmacia & Upjohn

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

September 6, 1996

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
Regulatory Manager
U.S. Market Company-Regulatory Affairs

DWC:rlc

Attachments
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

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:aced

Attachments

RECEIVED
FEB 18, 1997

GENERIC DRUGS