CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 4652/S8

APPROVAL LETTER

AUG 29 1986

NDA 4652/S-008

Progynon Associates
Attention: Mr. Wm. Cameron McEwen
Managing Director
9300 Wilshire Blvd., #500
Beverly Hills, CA 90212

Dear Mr. Cameron:

Reference is made to your supplemental new drug application dated December 14, 1984, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation T (brand of testosterone pellets, USP, 75 mg).

We also refer to your final printed labeling dated July 29, 1986.

The supplemental application provides revised labeling, and manufacturing and controls information as requested in our letter of May 29, 1984, regarding Supplement 7.

We have completed the review of this supplemental application as amended, and it is approved, effective on the date of this letter. We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

/S/ 8/28/86

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: Orig NDA
HFN-810
HFN-801 + labeling
HFN-231 + labeling
HFN-83 + labeling
HFN-810/MBennett
HFN-810/LRipper/8-20,26-86/2035R
R/D Init by MBennett/8-20-86/DKertesz/CSchaffenburg/8-21-86/JGueriguian/8-26-86

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4652/S8

FINAL PRINTED LABELING

Labeling: ORIG
NDA No: 4652 Date: 8-5-76
Reviewed by: M Bennett

Progynon Associates - 9300 Wilshire Blvd. #560 - Beverly Hills, CA 90212

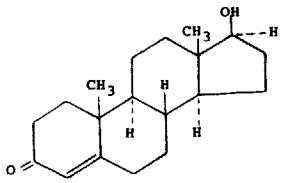
brand of testosterone
Pellets USP for Subcutaneous Implantation

Product Information

DESCRIPTION: T pellets for Subcutaneous Implantation contain testosterone, USP, in densely compacted pellets to provide prolonged release of the androgenic steroid.

Androgens are steroids that develop and maintain primary and secondary male sex characteristics, and are derivatives of cyclopentanoperhydrophenanthrene. Endogenous androgens are C-19 steroids with a side chain at C-17, and with two angular methyl groups. Testosterone is the primary endogenous androgen. In their active form, all drugs in the class have a 17-beta-hydroxy group.

Chemically, testosterone is 17-hydroxyandrost-4-en-3-one, with the empirical formula $C_{19}H_{28}O_2$, a molecular weight of 288.4, and the following structural formula:



MKB

Testosterone is a white to slightly creamy-white, odorless, crystalline powder. It is almost insoluble in water; soluble in 5 parts of ethanol, and in 2 parts of chloroform.

Each T Pellet contains 75 mg testosterone, USP, without binder, diluent or excipient. The Pellets are cylindrical, measuring 3.2 mm in diameter and approximately 8 to 9 mm in length, and each Pellet weighs 75 mg. T Pellets are sterile and ready for subcutaneous implantation.

CLINICAL PHARMACOLOGY: Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum: the development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature, and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, phosphorus, 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 the eventual termination of linear growth which is brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause a 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 the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

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

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

Pharmacokinetics: Testosterone given orally is metabolized by the gut and 44 percent is cleared by the liver in the first pass. Oral doses as high as 400 mg per day are needed to achieve clinically effective blood levels for full replacement therapy.

Densely compacted pellets of testosterone, such as T Pellets, have been formulated for subcutaneous implantation to provide an efficient source from which a steady rate of absorption of the steroid can continue for prolonged times.

Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about two 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. As reported in the literature, the half-life of testosterone varies considerably, ranging from 10 to 100 minutes.

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: In the male: T Pellets are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:

Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.

Hypogonadotropic hypogadism (congenital or acquired) - idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be obtained every 6 months to assess the effect of treatment on the epiphyseal centers. (See **WARNINGS**.)

CONTRAINDICATIONS: T Pellets are contraindicated for use in men with carcinomas of the breast of with known or suspected carcinomas of the prostate. T Pellets are contraindicated in women who are or may become pregnant. T Pellets may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

WARNINGS: Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma (See **PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility***). Peliosis hepatis can be a life-threatening or fatal complication.

Cholestatic hepatitis and jaundice occur with 17-alpha-alkylandrogens (such as methyltestosterone) at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

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

Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

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 heights.

Exogenous testosterone has been suggested to play a causal role in the sleep apnea syndrome.

PRECAUTIONS: ***General:*** Priapism or excessive sexual stimulation may develop. Males, especially the elderly, may become overstimulated. Oligospermia and reduced ejaculatory volume may occur after prolonged administration or excessive dosage.

Information for Patients: The physician should instruct patients to report any of the following side effects of androgens:
Too frequent or persistent erections of the penis. Any nausea, vomiting, changes in skin color or ankle swelling.
Any male adolescent patient receiving androgens for delayed puberty should have bone development checked every 6 months.

Laboratory Tests: Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.
Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

Drug Interactions: Anticoagulants C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulants. Patients receiving oral anticoagulant therapy require close monitoring especially when androgens are started or stopped.

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

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

Drug/Laboratory Test Interferences: Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clincial evidence of thyroid dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility - 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 for the development of prostatic hypertrophy and prostatic carcinoma. Information on mutagenesis is unknown.

Pregnancy: Teratogenic Effects - Pregnancy Category X: (See **CONTRAINDICATIONS**).

Nursing Mothers: It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, 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. (See **CONTRAINDICATIONS**.)

Pediatric Use: Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every 6 months by an x-ray of the hand and wrist (See **INDICATIONS AND USAGE,** and **WARNINGS**.)

ADVERSE REACTIONS: ***Endocrine and Urogenital Female*** The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman, androgens cause virilization of external genitalia of the female fetus.

Male: Gynecomastia, and excessive frequency and duration of penile erections. Oligospermia may occur at high doses. (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** General.)

Skin and appendages: Hirsutism, male pattern of baldness, 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 paresthesiae.

Metabolic: Increased Serum Cholesterol

Miscellaneous: Inflammation and pain at the site of subcutaneous implantation of testosterone containing pellets, and rarely anaphylactoid reactions. May induce sleep apnea (See **WARNINGS**).

OVERDOSAGE: Overdosage of medication may be reflected in the occurrence of the signs and symptoms associated with testosterone-anabolic drugs. Nausea and early appearance of the manifestations of edema should be looked for. However, there has been no report of acute overdosage with androgens.

DOSAGE AND ADMINISTRATION: Dosage must be strictly individualized. The suggested dosage for androgens varies depending on the age, sex, and diagnosis of the individual patient. Adjustments and duration of dosage will depend upon the patient's response and the appearance of adverse reactions.

Dosage regulation is less flexible with pellet implantation than with oral or parenteral administration. Pellets should be implanted only after oral or parenteral dosage has been established. The suggested average dose of T Pellets for Subcutaneous Implantation at each administration is two (150 mg) to six pellets (450 mg) which usually last for three to four months and sometimes six months. The duration of therapy will depend upon the response of the condition and the possible appearance of adverse reactions.

The Pellets may be implanted by using an injector, or by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure; aseptic precautions must therefore be observed.

By Injector: The pellets may be implanted quickly and easily by means of the Kearns Pellet Injector. The areas usually selected for implantation are the infrascapular region or the posterior axillary line. Aseptic precautions must be observed as for any surgical procedure. Careful cleansing of the skin should be followed by the application of antiseptics, such as iodine and alcohol. The area should be infiltrated with procaine solution 1:100. Make a very small incision (about 2 mm long and 1 mm deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The needle of the injector, with sharp plunger in place, should be inserted into the incision and gently forced to the desired site of implantation in the subcutaneous tissue. The sharp plunger should be withdrawn, and one or two Pellets inserted into the hollow needle. The simplest method for placing the Pellets in the needle is to allow the Pellet to slide from the vial in which it is packed into the slot in the needle. The Pellets are pushed as far as possible through the needle by means of the blunt plunger and held in place with a plunger while the needle is gently withdrawn. When the needle comes in contact with the knob of the plunger, both are withdrawn. It is considered advisable to implant no more than two Pellets in each pocket. Where more than two Pellets are implanted, the procedure is repeated, using the same scalpel incision for the entrance of the needle, but pointing the needle in a different direction, radially from the first implant. After the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient.

By Incision: The infrascapular region or the posterior axillary line are convenient sites for implanting Pellets. The operative field should be prepared in the usual manner with antiseptics such as iodine and alcohol and the area infiltrated with procaine 1:100 solution. An incision about one centimeter in length should be made. With blunt dissection, prepare a pocket about two centimeters in depth in the subcutaneous tissue below and away from the incision. Most operators prefer to make a separate, small pocket for each Pellet to be inserted. The edges of the pocket may be held apart by a small dilator and the Pellet inserted to the bottom of the pocket with small forceps. Force should not be used in inserting T Pellets. Close the incision with one or two sutures.

At times the Pellets slough out. This is usually traceable to superficial implantation or to insufficient aseptic precautions.

HOW SUPPLIED: T Pellets for Subcutaneous Implantation, 75 mg (See also **DESCRIPTION**) one Pellet per vial; box of three vials (NDC-52129-000-01); box of ten vials (NDC-52129-000-02).

REVISED 08/84
FINAL DOSAGE FORM
MANUFACTURED BY
SCHERING CORPORATION
MADISON, NEW JERSEY 07940

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4652/S8

MEDICAL REVIEW(S)

NDA 4652 (s-008)
Oreton pellets
Progynon Assoc.

Review and Evaluation of Clinical Data

1. Name of Drug: Trade: Testosterone pellets, USP

2. Dosage Form and Route of Administration:

   75 mg pellets for subcutaneous implantation.

3. Category or Use of Drug:

   Androgenic Steroid

4. Date of Submission: December 14, 1984

5. Reason for Submission: Final printed labeling bearing the date of August 1984.

6. Summary Evaluation:

   In this revised FPL the sponsor has incorporated changes recommended in our letter of May 29, 1984. However, this revised labeling is unacceptable, because the letter size is smaller than usual, making it difficult to read. The sponsor was informed about the letter size in our letter of may 1984.

7. Conclusion and Recommendation:

   The revised FPL bearing the date of August 1984 contains changes recommended in our letter of May 29, 1984. However, this revised FPL is unacceptable, because of the smaller than usual letter size which makes it difficult to read.

/S/

S. N. Dutta, M.D.

2-13-85

cc:
Orig. NDA
HFN-810
HFN-340
HFN-810/SNDutta/CJ/2/12/85
Wang No. 0604D

Dated mail letter MKB

FEB 13 1985

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4652/S8

CORRESPONDENCE

NDA 4652/S-008

JUL 18 1986

Progynon Associates
Attention: Mr. William Cameron McEwen
Managing Director
9300 Wilshire Blvd., #500
Beverly Hills, CA 90212

Dear Mr. McEwen:

Reference is made to your Supplemental New Drug Application dated December 14, 1984, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation T (brand of testosterone pellets, USP, 75 mg).

We also refer to our letter of October 8, 1985, which stated that although the wording in the revised package insert is acceptable, the letter size is unacceptably small. We note that the insert included in your periodic report dated June 9, 1986, contains a suitably revised package insert. Please submit twelve copies of the labeling to Supplement 8 so that we may complete our review of that supplement.

Your cooperation is appreciated.

Sincerely yours,

pp for 7/17/86

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: Orig NDA ✓
HFN-810 lwr 7.17.86
HFN-810/LRipper/7-17-86/1857R

GENERAL CORRESPONDENCE

OCT 8 1985

NDA 4652/S-008

Progynon Associates
Attention: Mr. Wm. Cameron McEwen
Managing Director
9300 Wilshire Boulevard, Suite 560
Beverly Hills, CA 90212

Dear Mr. McEwen:

Reference is made to your supplemental new drug application dated December 14, 1984, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation T (brand of testosterone pellets, USP, 75 mg).

The supplemental application provides revised labeling and manufacturing and controls information as requested in our letter of May 29, 1984, regarding Supplement 7.

The labeling has been revised as requested in our letter and, although the wording is considered to be acceptable, the letter size is unacceptable under Section 502(c) of the FD&C Act and 21 CFR 201.15(a)(6). Please submit revised labeling. If final printed labeling is submitted, twelve copies should be provided rather than the three required for draft labeling.

Your cooperation is appreciated.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: Orig NDA
HFN-810
HFN-810/SDutta/MBennett
HFN-810/LRipper/9-20-85/0561R lr 9-24-85
R/D Init by REastep: 9/20/85
Concurrence: MBennett/9/20; Kertesz, Dutta. Troendle/9/24/85
REVIEW/WAITING FIRM
Note to document room: Change drug name to T (testosterone pellets)

NDA SUPPLEMENT

PROGYNON ASSOCIATES

C R 14

December 14, 1984.

NDA NO. 4652 REF. NO. S-007

NDA SUPPL FOR [redacted] & CONTROLS

Solomon Sobel, MD
Director
Division of Metabolism and Endocrine Drug Products
FDA
Rockville, MD 20857

4 cc HDC
1 MKB

RE: NDA 4652/S-007

Dear Dr Sobel,

I attach the following information concerning our testosterone pellet product:

1. An original and three copies of the product insert which was immediately revised in accordance with the instructions in your letter of May 29.

2. A letter from Schering Corporation certifying that the manufacture of the product remains the same as it was when the product was approved.

Schering manufactures the pellets and packages them in individual sealed glass vials as specified in the NDA. The vials are then shipped to
where they are labeled and packaged in boxes of ten. The boxes are also labeled.

The pellets are held in a special area in shipping department, from which they are sent to physicians, pharmacies and hospitals.

master file may be referenced for its packaging controls:

Yours truly,

Wm. Cameron McEwen
Managing Director

RECEIVED
HFN-810
DEC 20 1984
CENTER FOR DRUGS AND BIOLOGICS

9300 WILSHIRE BOULEVARD, SUITE 560, BEVERLY HILLS, CA 90212 (213)859-0875

PROGYNON ASSOCIATES

9300 Wilshire Blvd #500
Beverly Hills, Ca 90212

SUPPL NEW CORRES

June 12, 1986.

Center for Drugs and Biologics, HFN-810
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

NDA #4-652
S - 008

Ladies/Sirs:

I attach a copy of our receipt for supplement # S-008 for the above NDA.

The agency replied to our submission saying that the wording of our insert was approved, but that the print would need to be enlarged.

We have increased the size of print and will be submitting a sample to the agency. But we have misplaced the agency's letter specifying this.

Can you send us a copy for our records? It will be numbered S-008 and dated early in 1985.

Thank you for your help with this matter.

Yours truly,

Wm. Cameron McEwen
Managing Director

REVIEWS COMPLETED

CSO ACTION: Cy. of ltr. sent under back
LETTER ☐ N.A.I. slip

lwr 6.19.86
CSO INITIALS DATE

RECEIVED
HFN-810
JUN 19 1986
CENTER FOR DRUGS AND BIOLOGICS

PROGYNON ASSOCIATES

SUPPLEMENT FILE

July 29, 1986.

Noted, as per my note of 7/15/86, file label is correct.
CMA. 8/18/86

Solomon Sobel, MD
Director, Div of Metabolism
and Endocrine Drug Products
HFN-810
FDA
Rockville, MD 20857

RE: NDA 4652/S008

Dear Dr Sobel,

I attach twelve copies of our T pellet insert.

I apologize that these were not sent to you earlier. The insert was revised immediately following your letter of October 8, 1985.

Yours truly,

Labeling Technically Satisfactory 8/18/86 RMCB

Wm. Cameron McEwen
Managing Director

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER 8/29/86 ☐ N.A.I.

CSO INITIALS 2/29/88 DATE

RECEIVED
HFN-810
AUG 5 1986
CENTER FOR DRUGS AND BIOLOGICS