CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-791

MEDICAL REVIEW(S)

DEC 8 1997

NDA 20-791
MOR complete: December 5, 1997
Regarding: Draft Package Insert and Draft Patient Instructions for TESTODERM® AT (Testosterone Transdermal System).

Medical Officer Review of Draft Label

Background: The sponsor submits the revised draft package insert and patient instructions for review. This label has been constructed based on modifications to the initial draft following the Division's recommendations. Below are summarized the clinical recommendations based on review of the new submission. These will be transmitted by fax to the sponsor.

The following recommendations pertain to the draft package insert:

Mark S. Hirsch, M.D.
Medical Officer
DRUDP

12/8/97

cc: Orig NDA 20-791
Division File/HFD-580
HFD-580/LRarick/HJolson/MHirsch/TRumble

NDA 20-791
MOR complete: October 14, 1997
Regarding: Draft Package Insert and Draft Patient Instructions for TESTODERM® AT (Testosterone Transdermal System).

OCT 15 1997

Medical Officer Review of Label and Patient Instructions

Background: The sponsor submits the draft package insert and patient instructions for review. This label has been constructed based on modifications to the existing package insert for TESTODERM® and TESTODERM® with ADHESIVE. Below are summarized the clinical recommendations based on review of the submission. A regulatory letter will be drafted to convey these recommendations to the sponsor.

The following recommendations pertain to both the draft package insert and the draft patient instructions:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Mark S. Hirsch, M.D.
Medical Officer
DRUDP
Concur - 10/15/97
cc:
Orig NDA 20-791
Division File/HFD-580
LRarick/HJolson/DShames/MHirsch/TRumble/HFD-580

MEDICAL OFFICER'S REVIEW OF TESTOSTERONE
(Testoderm -II)
NDA 20-791

Table of Contents

1 Title and General Information

1.1 Medical Review

1.1.1 NDA 20-791

1.1.2 M.O. Review

1.1.3 Submission December 26, 1996

1.1.4 Review completed - September 1, 1997

1.2 Drug name

1.2.1 Generic name Testosterone

1.2.2 Proposed trade name - pending Testoderm® - II

Testoderm®- AT (arm/torso application) not acceptable

1.3 Sponsor: Alza Corporation

1.4 Pharmacologic category: androgen

1.5 Proposed Indication:

Indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

1.6 Dosage form and route of administration:

Transdermal system applied to nonscrotal areas
Testoderm with a daily application of 60 cm^2 system to deliver 6 mg/day

The currently marketed scrotal Transdermal systems include: Testoderm® 40 and 60 cm size delivering 4 or 6 mg/d respectively and the Testoderm® with adhesive - 60 cm size .

The system is composed of layers:

- flexible backing of transparent polyester/ethylene-vinyl acetate copolymer film,
- a drug reservoir of testosterone and 1.2 mL alcohol USP gelled with hydroxypropyl cellulose
- an ethylene-vinyl acetate copolymer membrane coated with a layer of a polyisobutylene adhesive formulation that controls the rate of release of testosterone from the system
- a protective liner of silicone-coated polyester which must be removed before application of system.

1.7 NDA Drug Classification - S

1.8 Important Related Testosterone Delivery Systems

- **Transdermal preparations**

ALZA Testoderm System

Available in two sizes to deliver 4 or 6 mg testosterone for one day. The 40 cm^2 contains mg testosterone and 60 cm^2 contains mg to be used for one day. Extensive metabolism from testosterone to dihydrotestosterone in the scrotal skin. (NDA 19-762)

Theratech Androderm

Androderm Testosterone Transdermal System - non-scrotal patch. Each patch is designed to deliver 2.5 mg of testosterone per system per day using a 7.5 cm central drug delivery reservoir on non-scrotal skin. The majority of patients require two systems per day to delivery a total dose of 5 mg/day with a small percentage of men requiring three systems. (NDA 20-263)

3M Pharmaceuticals - IND

Propionate

- Eli Lilly - Propionate injection USP 50 mg/mL (8-254)
- generic Steris Laboratories doses 25,50 and 100 mg/mL (old - Perandron - Ciba - 9349)

Cypionate

- Upjohn - DEPO-testosterone two strengths in cottonseed oil doses of 10 and 200 (NDA 17-968)
- Generic - Virilon IM /Star

Under investigation:

*

Halotestin - Upjohn (NDA 10-611)
Ora-testryl tablets - Squibb (NDA 11-359)

Methyltestosterone

Android - Brown Pharm

Oreton - Schering - (NDA 3-158 - approved January 6, 1941)
Virilon - Star

Microcapsular and Sublingual (hydroxypropyl)

Gel - approved in France as Andractim (generic androstanolone or stanolone (see review by Dr. de Lignieres).

Sustenon - Marketed in Scandinavia - as a mixture of Testosterone esters.

- **Anabolic Steroids**

Nandrolone phenpropropionate - Durabolin - breast cancer

Nandrolone decanoate - Deca-durabolin - anemia of renal insufficiency.

Ethylestrenol
Maxibolin - Organon

Oxandrolone - Oxandrin (old name - Anavar)

Oxymethelone

Anadrol - approved for hypoplastic anemia Syntex

Stanozolol - Winstrol indicated for the treatment of hereditary angioedema. **(12-885)**

1.9 Related Reviews - see statistics, biopharm, and chemistry.

2 Table of Contents - see page 1

3 Material Reviewed (volume numbers which serve basis for this review)

Electronic versions submitted by sponsor
volume 1.1 - the entire NDA is well indexed.

Volumes Reviewed

Volume	Trial	Date
Volume 1.1	Application Summary	December 26, 1996
Volumes 1.2, 1.30-1.45, 1.53	Clinical Review	

4 Chemistry/Manufacturing Controls
See Chemistry review

5 Animal Pharmacology/Toxicology
See Pharmacology review

6 Clinical Background

Androgen History

The history of androgen began with the identification and understanding of the Leydig Cells in the testis. Although the importance of castration has been known since antiquity, when the removal of the testicles of a male animal resulted in the reduction or loss of male sexual characteristics, the discovery and purification of testosterone was not accomplished until the late 1930s.

Franz Leydig, a German histologist, originally described the testicular interstitial cells called the Leydig Cell in an 1850 paper which he published while a lecturer at Wurzburg University. This was long before the endocrine function of the testes was understood. The interstitial cells, or Leydig cells, were discussed as part of a comparative study of male reproductive histology in various mammals. In this paper he made comments on some aspects of the testis and to the prominent clusters of what appeared to be cells that had been overlooked by previous researchers which he found consistently between the seminiferous tubules.

A later paper by Friedrich Reinke in 1896 detailed the fine histological crystalloids found in the human Leydig cells. One early concept was that the Leydig cells took up materials from the circulation, processed them,

and then passed these nutrients to the adjacent seminiferous tubules to support spermatogenesis. The important endocrine function of testosterone was to come much later.

In 1889. Dr. Brown-Sequard, a professor at the University of Paris, injected extracts of animal testes into himself and claimed rejuvenation. This 'scientific experiment' led the way to the marketing at the turn of the century of the 'orchis' products supposedly from animal testicular extracts. Many of these orchis products are still available today as food products.

The first important endocrine experiments, however, were conducted by Berkhold, and involved the testicular transplantation in male chickens 2-3 months old. It is presumed that the transplanted testis were sometimes able to become established with a vascular supply. The testicular transplanted animals exhibited male sexual characteristics of roosters which included the full comb and wattle development. Berkhold used this is as proof that the testicular tissue was the hormonal factor and not a function of innervation. The androgenic or bioavailable effect refers to the transformation of the Capon's comb (the wattles) to the Roosters comb (cocherel).

In 1903, Bouin and Ancel published that it was most likely that, as in the thyroid, these interstitial cells produced unknown products, which were transported through lymph to the blood and probably carried out unknown functions. A second paper in 1901 by Regaud and Policard, using the pig testis, noted that there was probably a relative anatomical and functional independence between the interstitial cells and the seminiferous tubules.

A common textbook of 1917 notes that the so-called internal secretion of the testicles has been studied anew of late years in connection with the discussion over the propriety of castration for hypertrophy of the prostate. "It has long been known that the testicles are essential to a virile adolescence, since castration in infancy produces the recognized type of high-voiced, effeminate eunuchs. The familiar contrast between ox and bull, horse and stallion, is equally to the point. (*Edward L Keyes, Jr, MD, PhD. Urology. New York and London: D Appleton and Company, 1917.)*

Scientist	Year	Discovery
Berkhold	1849	First Endocrine Experiment
Leydig	1850	Testicular Interstitial Cells (Levdig Cells)
Sertoli		Nurse cells (Sertoli Cells)
Reinke	1896	Leydig Cell crystalloids
Brown-Sequard	1889	Rejuvenation
Bouis and Ancel	1903	Endocrine function of Testis

Bremner	1983	Circadian

Testosterone is primarily produced by the Leydig cells in the testis and the daily production of testosterone is about 4 to 8 ng daily. 95% of the testosterone is secreted by the Leydig cells in the testis. 5 - 7% of the androgens which are metabolized to testosterone are secreted by the adrenal gland as dehydroepiandrosterone (DHEA and DHEAs). There are approximately 500 million Leydig cells secreting approximately 6 - 7 ng/day of which 98% is protein bound and 2% free (.2 nM). Testosterone is bound to sex hormone binding globulins (SHBG) and only small amounts are available to androgen receptors. Testosterone is rapidly metabolized with a half life 12 minutes.

Testosterone levels peak in the morning, decreasing during the day (Bremner et al 1983; Nieschlag 1974). The peak and nadir levels differ by approximately 30%. This diurnal rhythm noted early in puberty may be lost with age Supporters of transdermal delivery of testosterone believe that this better approximates the diurnal rhythm in men. There also appears to be significant progressive decreases in total serum testosterone with age (Blackman et al 1988). In the older male this gradual decrease in androgens may be associated with loss of muscle mass and strength, bone density loss and decreased virility. There may be cultural differences in androgen levels, metabolism and the androgen receptors. (identify when diurnal rhythms first identified)

Other major active metabolites of testosterone include 17 *beta* estradiol and 5 *alpha* dihydrotestosterone (DHT) by aromatization or reduction, respectively. DHT is not metabolized to either testosterone or estradiol.

The current understanding of the androgens is more complex with the understanding of the alterations in the androgen receptors that are necessary of testosterone activity. The androgen receptor is a member of the steroid/thyroid receptor gene family. Although not as well understood as the estrogen receptor mutations are associated with prostate cancer and the agonist effect of some antiandrogens would suggest unique subtypes for the androgen receptor as has been identified with the estrogen receptor. Most mutations of the androgen receptor gene result in phenotypic abnormalities of the male sexual development. Many of these mutations have been carefully studied with analysis of the androgen resistance syndromes, e.g. testicular feminization (McPhaul et al JCEM 76:17-23, 1993 and Wilson , Biol of Reproduction 46: 168-173, 1992). Additional receptor mutations have been noted with prostate cancer cells (Wilson, NEJM) and particularly with alterations in the agonistic response with antiandrogens (Murphy).

Many important enzymes are regulated by androgen. These include the androgen receptor, prostate specific antigen (PSA) , the p450 system and the apoptosis genes (TRPM2). Androgen deprivation, e.g., castration either medical or surgical, is followed by decrease in the PSA activity prior to apoptosis of the androgen dependent cells. All of these enzymes contribute to the variability of response to androgen suppression and tumor regression.

Disorders associated with abnormal testosterone levels:

The prevalence of hypogonadism has been estimated to be approximately 1% in men 20 - 50 years of age (Montanini, 1988). Dr. Tenover (1988) estimated that 25 - 50% of men over the ages of 65 are hypogonadal

Primary hypogonadism in which the dysfunction is in the testis.

Primary testicular failure affects 5 - 10% of the male population; this includes those with infertility. Less common causes are bilateral cryptorchidism, myotonic dystrophy, polyglandular failure, gonadal dysgenesis, vanishing testis syndrome, and autoimmune testicular disease. Other acquired etiologies include surgical or blunt trauma, testicular torsion, irradiation, chemotherapy, and infections. Aging, hepatic cirrhosis, and sickle cell disease probably reflect both primary and secondary hypogonadism. Androgen receptor defects are also important causes of testosterone deficiency which are not amenable to testosterone replacement.

Important examples of testicular failure include:

- Klinefelter's syndrome - (47 XXY). This "syndrome" was first described by Dr. Harry Klinefelter in 1942 with the report of 9 men with enlarged breasts, sparse facial and body hair, small testes and an inability to produce sperm. A decade passed before the chromosomal abnormality was further defined as associated with an extra sex chromosome. Although the chromosomal abnormality occurs as frequently as 1 in 500 to 1 in 1,000 male births not all men with the chromosomal abnormality will develop the Klinefelter's Syndrome.

  Kallmann's syndrome is a frequent example of hyper-gonadotropic hypogonadism which was first described by Dr. Kallmann. Recent research identifies the defect early in the neural development of the olfactory bulbs with the aberrant migration of neural cells.

Secondary hypogonadism or hypogonadotropic hypogonadism includes:

- Hypothalamic or pituitary origin

- Isolated LH or FSH deficiency
- Acquired gonadotropin deficiencies
- Prolactin-secreting pituitary tumors
- Severe systemic illness
- Uremia
- Hemochromatosis
- Sickle cell anemia
- Rheumatoid Arthritis
- and other chronic diseases, e.g. HIV/AIDS

Age should not be assumed to be associated with hypogonadism; one should look for an underlying endocrine or non-endocrine pathology as the cause of hypogonadism. Earlier studies identified men with decreased serum testosterone levels primarily from clinics and nursing homes which may not have been a reflection of a healthy aging population. *(Neaves et al - JCEM 59:756 - 1984;Blackman, M R, R D Weintraub, S W Rosen, and S M Harman. "Comparison of the Effects of Lung Cancer, Benign Lung disease, and normal aging on pituitary-gonadal function in men." J Clin Endocrinol Metab 66 (1988): 88-95; Handelsman D J (1985) Endocr Rev 6: 151)*

Replacement therapy:

The aim of androgen replacement therapy is to achieve a physiologic dose of testosterone and in the same 'natural' physiological pattern. The testosterone circadian rhythm, with an early morning peak and evening nadir ,is unique in man. It was first recognized (check) *(see Bremner, 1983 - JCEM 56, 1278-1281 and Nieschlag, 1974 - Hormone Research 7: 138-145).*

Preparations containing unapproved animal testicular extracts or dried "androgen powder" are still being manufactured and available. The testosterone content of these preparations is fairly low since the testis, in contrast to other endocrine glands, does not store the hormonal secretory products. At best these compounds exert placebo effects.

The testosterone molecule is a steroid with three 6 member rings and one 5 member ring built from the cholesterol molecule. Oral preparations of androgens or anabolic steroids are usually alkylated at the 17th *alpha* position while parenteral compounds are esterified. All anabolic steroids with this steroid conformation are androgenic and all androgens are probably anabolic. It is not possible to differentiate between the two functions.

Four to six hundred mg of testosterone must be administered daily in hypogonadal men if the patients are to be substituted by oral testosterone and replace the 7 mg per day that is produced normally (Horton J Cl Inv

45: 301-313, 1966). Free testosterone is absorbed well from the gut but is effectively metabolized and inactivated in the liver before it reaches the target organs as a first-pass-effect. Only when it exceeds the 30-fold the amount of testosterone produced daily by a normal man (e.g. 200 mg) is the metabolizing capacity of the liver overruled. For this reason, oral administration of free testosterone has not become a generally accepted method for therapeutic purposes, eg., Oreton - methyltestosterone. Until recently the gold standard of androgen replacements for hypogonadal men was by depot, e.g. testosterone enanthate, propionate or cypionate. These depots appear to behave in a similar manner (Nankin et al Fert Steril 46: 300-307, 1986). The development of transdermal testosterone delivery systems, both scrotal and nonscrotal, has provided a new more acceptable method to provide replacement therapy at more physiological levels.

There are a large number of men requiring testosterone replacement. The current estimates are increasing with the growing realization that the aging male population may also need hormone replacement therapy (HRT). Androgen delivery systems are therefore a booming business.

Androgen Dependent systems:

Reproductive System

The prostate is dependent on androgen and, in particular dihydrotestosterone activity. Although Benign Prostatic Hyperplasia (BPH) and Prostatic Carcinoma (PCA) are both androgen dependent, other factors also play a role in the development of these diseases. To date no prostate cancer has been identified as the result of androgen replacement at physiological levels. The importance of androgen replacement for other reasons including reproductive function outweighs the possible risk but the patient should be aware of this fact .

Testosterone has a major impact on male reproductive function and sexuality. Maintenance of reproductive function - e.g. sexual arousal and arousability during erotic film stimulation as measured by penile tumescence have been directly associated with circulating testosterone levels (Davidson et al JCEM 57: 71, 1983 and Anderson, Bancroft and Wu, J C E M 75: 1503-1507, 1992). Sexual interest and arousability appear to benefit the most from testosterone replacement. Higher levels of sexual activity during aging have been associated with higher levels of total testosterone. Decreased levels of testosterone, and free testosterone, has been associated with reduced sexual activity and includes self-reported frequency of masturbation.

Non-reproductive system functions:

• Metabolic functions which include nitrogen balance, muscle mass, lipid and carbohydrate metabolism and electrolyte changes. Of these, muscle mass has been studied in this submission. The body weight increases are secondary to an increase in muscle mass and retention of sodium and water. The muscle in the shoulder region and pectoral muscles are those most responsive to androgens. Muscle mass increase has been associated with increasing muscle protein synthesis without significant increase in muscle fiber diameter (Griggs et al 1989 J appl Physiol 66:498-503). The perceived increase in muscle mass is a major reason for the abuse of androgens. (Bhasin et al NEJM 335:1- 7, 1996).

• Respiratory System:

One to four percent of the population have some form of Obstructive Sleep Apnea (OSA). Sleep apnea is usually seen in middle aged and obese men and in a small number of cases has been associated with testosterone for the induction or worsening of obstructive sleep apnea. In the cases reported the testosterone levels have been at superphysiological levels (Matsumoto et al 1985 Clin Endo 22:713-721). It is not clear if this is caused through a central or peripheral mechanism which can result in possible upper airway collapse.

• Erythropoiesis

Since the early 1970s it has been established that androgens stimulate erythropoiesis. Both human and animal studies have demonstrated increases in hemoglobin, reticulocyte count and bone-marrow erythropoietic activity with the administration of androgens (Shahidi NEJM 289:72-80, 1973). The normal hemoglobin, hematocrit and red-cell count is higher in the adult male than the adult female and thought to be secondary to androgen. These differences are not present prior to puberty. Likewise hypogonadal men also demonstrate a decrease in the number of circulating erythrocytes and in the hemoglobin concentration which can be corrected after the administration of androgens. Androgens were for many years the most useful nonspecific erythropoietic stimulant available (see 1962 labels and refer to anabolic steroids approved for 'anemia'). Today this role has been supplanted by EPO. Although recent problems with cost have again encouraged the use of androgenic steroids (Scand J Urol Nephrol 1996 30:403-8).

The average life span of a red blood cell is 120 days and without continual replenishment one should see decreasing counts by four months. Although the upper limit has been established as approximately 50% hematocrit (HCT), it is not clear what is the

acceptable lower limit. All approved testosterone replacement therapies appear to maintain the hemoblogin and hematocrit within normal clinical parameters. The following chart identifies the normal clinical parameters.

Significant increases in whole body hematocrit and red blood cell volume while on 300 mg intramuscular every 3 weeks testosterone enanthate with an increase in red blood cell volume and a decrease in plasma volume. Androgens influence the synthesis of erythropoietin and therefore there is a direct increase in the production of red blood cells. The abuse of androgens can probably lead to blockage of many small vessels, especially intracerebral. Mortality due to cardiovascular disease is 5 - 6 times higher in men than in premenopausal women thought to be attributable to androgens. All androgen therapy should be monitored by periodic blood counts. Hemoglobin increases by about 1 g/dL with pharmacological doses.

	RBC ml/ml	Hgb (g/dL)	Hct (%)
Female	3.8-5.1	12-16	36-46
Male	4.3-5.3	13.5-17.5	39-49
6-12	4 - 5.2	11.5-15.5	35-45

There is evidence that normal physiological levels of testosterone are maintained while on transdermal testosterone delivery systems.

- Cardiovascular changes and stroke potential

Testosterone, when used in normal physiological doses in healthy individuals, rarely has adverse side-effects. However supraphysiological levels are clearly associated with changes. It has been estimated by Krauss that hematocrit increases greater than 50% may increase blood viscosity three to fourfold (J Urology 1991 146:1566-70).

- Lipid profile alterations - Androgens and anabolic steroids are thought to be associated with decrease in high density lipoproteins and sometimes with increase in the low density lipoproteins. This should be monitored while on androgen therapy. It is thought that there is a strong negative association between levels of testosterone and those of high density lipoproteins. Normal men have a lipid profile that puts them at greater risk for atherosclerosis when compared to women. (lower HDL and higher LDL). A depressed ratio of HDL to LDL is believed to be associated with accelerated atheroslcerosis.

It has been suggested that the changes in lipoprotein cholesterol may be dependent on the metabolic activity of the androgen, e.g. aromatization of testosterone enanthate Friedl (Metabolism 39:69-74, 1990).

• Liver disorders - Any testosterone replacement that passes through the liver, e.g. 17 alpha alkylated androgens, may impair liver function. With oral administration of testosterone 44% is cleared by the liver in the first pass. Liver changes have not been noted with transdermal delivery of testosterone. Testosterone undeconoate passes into the lymphatic system first. (what is the path of sublingual?)

• Prostate disease - Prostate growth is androgen dependent and should be monitored while patients are on androgen replacement. To date treatment appears to have resulted in prostate volume and prostate specific antigen levels comparable to age-matched normal men (Behre et al Clin Endo 40:341-349, 1994).

• Gynecomastia can result from increased peripheral aromatization to estrogen. It may also be related to inadequate metabolism of testosterone to dihydrotestoterone which may be seen in patients with Klinefelter's Syndrome as well as increasing levels of testosterone with aromatization to estrogen. The latter can be seen with the abuse of androgenic anabolic steroids as well as antiandrogens.

• Osteoporosis - There has been an increasing realization of the importance of androgen replacement in the older hypogonadal man. Some of the original work in this area was done by Dr.J. Tenover, now at Emory University. Although the incidence of osteoporosis in men is less than in women, at least 25% of all hip fractures occur in men. Osteoporotic fractures in men are a neglected public health problem. Treatment of either primary or secondary hypogonadism is a treatable cause of osteoporosis and should be excluded in all men presenting with spine or hip fractures. The benefits of androgen replacement in the elderly male population may extend beyond improvement in bone profile.

Bone development and maintenance appear to be decreased in hypogonadal men. Eunichs often develop osteoporosis (Albright and Reifenstein, 1948 in The parathyroid glands and metabolic bone disease. Williams and Wilkins, Baltimore pp 145-204). Men with inadequate bone development during maturation may have an increased risk for fracture (the fracture threshold)
(see Ann Int med 106: 354-461 1987 and JCEM 69 - 523 - 527 1989).
Alcohol excess can also be an attributable risk factor for osteoporosis in men . (Aust-Fam Physician 1997 26:135-43)

Bone density at a given age is determined both by the peak bone mass achieved at sexual maturity and the subsequent amount of bone loss. Androgens are a major determinant of bone mass in men. n both sexes spine BMD tended to increase with age. Therefore BMD changes vary by gender and skeletal site. Determinations of osteocalcin and N-telopeptide crosslinks at a single point in time may potentially be used as indicators of current bone status. ((Krall et al, J Gerontol A Biol Sci Med Sci 1997 Mar 52:M61-7).

It is important to understand if treatment of hypogonadal men will improve or normalize bone density measurements. One study noted that it may require additional therapy than serum testosterone within the laboratory reference range to normalize BMD and bone turnover (JCEM 1997 Feb 658-64). A study using spinal bone density as a function of time after orchiectomy in 12 men over a period of at least 3 years noted that bone density loss was more rapid during the first few years after castration it appeared (Stepan, JCEM 69:523-527, 1989). Alza has bone density studies with the scrotal transdermal system in progress.

- Transdermal skin irritations related to alcohol

Irritation from alcohol in transdermal systems appears to be a major factor in all transdermal systems and has been carefully studied in this submission. A review of the dermatitis related to alcohol both from occupational exposure and transdermal systems discusses the complex mechanisms of action of the irritation (Contact Dermatitis 25:1-6, 1993). There are estimates of 1 - 2% withdrawals from transdermal therapy due to the alcohol content of the systems.

- Testosterone - normal levels and assays

In most laboratories levels of testosterone ≤ 300 ng/dL (≤10.4 nmol/L) are thought to be consistent with testosterone deficiency. The free testosterone is approximately 1 - 2% of the total testosterone with a range between ng/dL nmol/L). However, it is not clear what portion of the total testosterone is still bioavailable to tissues.

All hormonal assays for the Theratech Androderm transdermal submission was measured in serum by the which served as the central laboratory for the analyses of the samples. Testosterone was measured by The minimum quantifiable was ng/dL and the sample volume needed was ml. Bioavailable

testosterone (BT) was measured by the separation of SHBG-bound steroid from albumin-bound with ammonium sulfate. The bioavailabe testosterone (BT) was the sum of the serum testosterone multiplied against the % non-SHBG bound steroid from the separation procedure. The minimum quantifiable was ng/dL Diydrotestosterone was done by ng/dl The accepted normal ranges in these studies are noted below.

All hormonal assays for the BCG Androtest submission were measured at

All hormonal assays for the Alza Testoderm submission were measured The lower limit of quantification for the testosterone assay was ng/dL.(contact Ms Cranley (703-893-5400 ex 5374.) parameters are: ng/dL for testosterone, ng/dL for dihydrotestosterone, pg/mL (men years of age and pg/mL men over 49 years of age for FT and pg/mL for E2

REFERENCE TABLE BY STAGE

Stage	Testosterone ng/dl	AGE - years
Tanner 1	<3 - 10 Mean = 4.9	<9.8
Tanner 2	Mean = 42	
Tanner 3	Mean = 190	
Tanner 4	Mean = 372	
Tanner 5	Mean = 546	
castrate - medical *	<15 ng/dL	
castrate-surgical**	< 30 ng/dL	

Source Endocrine Sciences Reference Ranges

** Santen J Clin Endocrinol Metab 1984: 58, 397.*

***After castration a 75% decrease in dihydrotestosterone is observed in prostate tissue.with a 90% reduction in circulating testosterone levels.*

Conversion Factors - International units v. ng/dl

Hormone	normal parameters	Conversion factors and number
FSH		1 ng = 3 mIU
LH	IU/L	1 ng = 7//8 mIU
Testosterone	m. ng/dL f. ng/dL	0.0347 m.10.4 - 34.7 nmol/L f. 0.68 - 2.78 nmol/L
Testosterone - free	M. ng/dL	0.0347 0.18 - 1.42 nmol/L
Dihydrotestosterone	M. ng/dL	0.0344 1.0 - 2.9 nmol/L

source - Becker 1990

THE NORMAL REFERENCES RANGES
Endocrine Sciences

Hormone	Unit	Mean≠SD	Lower Limit	Upper limit
Testosterone	ng/dL	620±185		
Bio T	ng/dL	239±84		
DHT	ng/dL	52±13		
Estradiol	ng/dL	2.1±0.7		
SHBG	ng/dL	1.04±0.52		
LH	IU/L	6.1±2.5		
FSH	IU/L	3.3±1.9		

6.1 Relevant human experience - See NDA 19-762 - the Alza Testoderm Scrotal System and NDA 20-263 - the Theratech nonscrotal Androderm system.

6.2 Foreign experience - none

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics - see Pharmacology and PK reviews.

6.5 Other relevant background information

IND
IND

6.6 Directions for Use - One to Two systems placed on the arm or torso (back or upper buttocks) daily.

APPEARS THIS WAY
ON ORIGINAL

8 **Clinical Studies**

The sponsor has submitted two pivotal studies, C95-044 and C95-045, as well as five supporting studies. The two pivotal trials are short in duration and designed to demonstrate the delivery of testosterone. Study C-95-044 included 22 men who entered the study ; 19 men were evaluable. This study was 7 days in duration. Study C-95- 045 included 13 evaluable men; 14 men entered the study. The duration of this second study was 8 days. Although the duration of these studies was brief there was ample evaluation to test the adequate delivery of testosterone. The supporting studies confirm the efficacy and safety of this product.

The sponsor submitted the following studies:

Protocol	Days/ N=evaluable	Type of Study
C-95-044-05	7 days/19	Pivotal*
C-95-045-05	8 days/13	Pivotal*
C-96-025-04	24 days/199	Topical safety
C-96-026-03	21 days/28	Topical safety
C-96-005-022	28 days/70	Androderm 5.0 mg* Testoderm-II 6 mg irritation
C-96-022-03	14 days/25	Androderm 2.5* Testoderm-II 6 mg irritation,tolerability in older men
C-96-048-01	4 days/8	Testoderm-II* pk/topical
C-96-079	5 days/21	Testoderm-II Wearing acceptability

* hypogonadal men - all others normal

8.1 Trial # C-95-044

Site	Investigators
Site 1:	**Mark S Kipnes, MD Sherwyn L Schwartz, MD Jerome S Fischer, MD Margaret A Vajdos** San Antonio, TX 78220
Site 2:	**Arshag D Mooradian, MD Alan B Silverberg, MD M Reza Rofougaran, MD** St Louis, Mo 63110
Site 3:	**Peter J Snyder, MD Abdallah Dlewati, MD** HUP, Philadelphia, Pa 19104

8.1.1 Objectives :

The sponsor stated that the primary objective of this study was to estimate the bioavailability of a new nonscrotal system applied to the upper buttocks and reference data from the original testosterone system applied to the scrotum. An important additional objective was to evaluate the topical profile effects of the new nonscrotal system. In addition, the sponsor evaluated the dose relationship of the one and two 60 cm^2 transdermal systems applied to the upper buttocks.

8.1.2 **Design**

This study submitted by the sponsor was a randomized, open label, four-period, crossover design with a lead-in placebo treatment followed by three active transdermal testosterone treatments each of which lasted 1 week.

The sponsor performed pharmacokinetic evaluations on days 7 and 8 of each of the active treatment periods. Blood samples were included before, during and after the application of the Day 7 active treatment.

The assigned treatments were:

Treatment A: placebo transdermal system 60 cm^2, containing no drug, worn on the scrotum

Treatment B: Testoderm 60 cm^2, containing 15 mg testosterone with a nominal delivery of 6 mg/day, worn on the scrotum

Treatment C: Testoderm -II 60 cm^2 Testoderm-II, 60 cm2 containing 328 mg testosterone with a nominal delivery of 4 to 7 mg/day, worn on the upper buttocks

Treatment D: Two Testoderm -II 60 cm^2, each containing 328 mg testosterone with a nominal delivery of 4 to 7 mg/day/system (8 to 14 mg total), worn on the upper buttocks

Twenty-two hypogonadal male patients were enrolled in this study. Of these nineteen patients completed the study. The mean age of those who completed the study was 55 years (range years). The sponsor states that the three patients who withdrew prematurely did so because of problems with blood sample collection during the placebo treatment.

8.1.3 Protocol

This study evaluated two formulations of testosterone transdermal systems in order to determine their relative bioavailability: Testoderm Testosterone Transdermal Scrotal System and Testoderm -II. The Testosterone Transdermal Scrotal System was the comparison system. The dose relationship of one and two Testoderm -II systems was evaluated. Testosterone (T), Dihydrotestosterone (DHT), free testosterone (FT), and estradiol (E_2) were measured for each application of the four treatments in 19 hypogonadal male patients.

Baseline hormone measurements were obtained from all patients during the placebo lead-in treatment period. Pharmacokinetic evaluations were performed on Days 7 and 8 of each active treatment period. Blood samples were obtained at frequent intervals immediately before, during, and after application of the Day 7 active treatments to determine the serum testosterone concentration-time profiles. Skin site assessments were performed on Day 8 during the Testoderm treatment period, and on Days 7 and 8 during the Testoderm -II and 2 x Testoderm -II treatment periods. There was no drug washout period between treatments.

Topical skin site evaluations and daily diaries of wearing acceptability were done. Identified skin site assessments were performed on Day 8 during the two treatment periods.

The entire study lasted for 3 weeks. Patients were required to stay in the research clinic facility one night for baseline study measurements during the placebo lead-in treatment period, and again at Day 7 of the

active treatment periods for pharmacokinetic and safety measurements.

The inclusion and exclusion criteria were satisfactory. The following are adapted from the sponsor's submission:

Inclusion Criteria:

Each volunteer was required to meet the following eligibility criteria in order to participate in the study:

- Hypogonadal males, 18 years of age or older, requiring testosterone replacement therapy for conditions associated with a deficiency or absence of endogenous testosterone;

- A history of primary or secondary hypogonadism and a history of total serum testosterone concentrations below 300 ng/dL;

- The patient was required to have used Testoderm 3 weeks prior to the initiation of the study. If the patient used other androgen testosterone replacement systems, he had to discontinue therapy prior to study initiation, as follows: testosterone enanthate or cypionate injections stopped use within 6 weeks; oral androgens stopped use within 1 week;

- Patients were to be healthy as determined by the screening procedures. Patients with clinically significant medical conditions could have been admitted to the study on a case-by-case basis after careful review of their medical history and laboratory findings. In such cases, any pre-existing or co-existing problems, clinically significant laboratory results, ailments, and/or treatments were documented in the appropriate case report form. The investigator and the sponsor approved entry of such patients into the study;

- A normal prostate; and

- Able to communicate effectively with study personnel and meet the requirements of the study procedures.

Exclusion Criteria:

- History or current diagnosis of prostate cancer, benign prostatic hyperplasia, or carcinoma of the breast;

- Known hypersensitivity to any components of the transdermal testosterone system;

- Uncontrolled hypertension or congestive heart failure;

- Chronic polycythemia (hematocrit greater than 55% or hemoglobin greater than 18 g/dL);

- Stroke or myocardial infarction within the past 6 months, or history of transient ischemic attacks;

- History of malignant hypertension, known left ventricular ejection fraction of less than 40%, or clinically significant cardiac arrhythmia;

- History of unexplained syncope or presence of hemodynamically significant obstructive valvular disease or hypertrophic cardiomyopathy;

- Any liver enzyme level more than twice the upper limit of the normal value;

- Serum creatinine above 2.0 mg/dL;

- Prolonged blood coagulation test results (ie, prothrombin time [PT] and partial thromboplastin time [PTT]);

- Any serious or life-threatening illness requiring regular medical treatment;

- Current alcohol intake greater than 14 drinks per week;

- Current use of drugs which may interfere with androgen metabolism (ie, spironolactone, finasteride, or ketoconazole), use of androgens other than Testoderm, or use of anabolic steroids (including longer duration injections or implants);

- Donation of blood/blood products within 45 days prior to study enrollment;

- Use of another experimental drug within 30 days of study initiation; and

- Inability or unwillingness to give informed consent.

8.1.3.1 Population,

There were a total of 22 hypogonadal men enrolled and 19 that completed this study. See the summary of patient demographics under 8.1.4.1

8.1.3.2 Endpoints

• To estimate the bioavailability of Testoderm-II applied to the upper buttocks using data from the Scrotal system as the reference.

• To evaluate the dose relationship of the one and two Testoderm-II systems applied to the upper buttocks.

The pharmacokinetic parameters of serum testosterone from two formulations of testosterone transdermal systems were evaluated in order to determine the relative bioavailability. The approved transdermal testosterone system was the Alza scrotal patch. See page 2 for the assigned treatments.

All blood sampling for pharmacokinetic assessment of hormonal assays were measured by

• To evaluate the topical effects of Testoderm-II

Skin site assessments were an important endpoint for these studies.
The patients returned to the clinic on Day 6 of the patch and the topical effects were evaluated at 1, 6, and 24 hours after removal of this system. The occluded skin was evaluated for any local reactions and adherence problems. Each patient completed a daily wearing acceptability diary which were returned to the clinic at the end of the week. The following tables include the skin assessment and adhesion rating scores.

Topical Effects Rating Scale

Score	Erythema	Edema, Papules or Pustules	Itching
0	None	None	None
1	Barely perceptible redness	≤50% of occluded area	Mild
2	Definite	≥50% of occluded area	Moderate
3	"beet"redness	N/A	Severe

Adhesion Rating Scores	
Score	Adhesion to skin
0	90% of system adhered to skin, no edges unattached
1	75-90% adhered
2	50-74% adhered
3	≤50% adhered or no longer adhered

- Clinical Laboratory Evaluations were performed at and included serum clinical chemistries, complete blood count, and Prostate specific antigen.

8.1.3.3 For Statistical considerations see statistical review.

8.1.4 Results

8.1.4.1 Patient Disposition

Nineteen patients completed the study. Twenty two patients were enrolled. Three patients terminated from the study during the placebo treatment due to sampling problems. The patients also had concomitant medications including thyroid replacement, oral corticosteroids and insulin.

The following table from the sponsor outlines the summary of the patients demographics in this study.

Summary of Patient Demographics

Baseline Variable	Patient Enrolled (n=22)	Patient Completed (n=19)
Age (Years) Mean ± SD (Min, Max)	54 ± 14.5	55 ± 14.0
Sex Male	22 (100%)	19 (100%)
Ethnic Origin		
Black	4 (18.2%)	3 (15.8%)
Caucasian	15 (68.2%)	13 (68.4%)
Hispanic	3 (13.6%)	3 (15.8%)
Height (cm) Mean ± SD (Min, Max)	176 ± 5.7	175 ± 4.9
Weight (Kg) Mean ± SD (Min, Max)	94 ± 18.6	96 ± 19.2

From sponsor's table

8.1.4.2 Efficacy endpoint outcomes

The sponsor notes that at steady state the means of the averaged serum concentrations of testosterone for the Testoderm-II system (one and two applications) were within the clinical range.

The means of the averaged serum concentrations (C_{avg}) of testosterone for one patch (T-II) and two patches (T-II) were 391 and 583 ng/dL, respectively. The mean maximum testosterone concentrations (C_{max}) were 570 and 941 ng/dL respectively. The mean minimum testosterone concentrations (C_{min}) for one and two systems were 201 and 326 ng/dL, respectively.

The means of the averaged serum DHT concentration values at Hours 0 and 24 for placebo, Testoderm (scrotal patch), T-II and 2T-II were 11, 134, 38, and 56 ng/dL, respectively. All were within the normal range. The mean serum DHT concentration values at Hour 4 for placebo, Testoderm , T-II and 2T-II were 9, 146, 47, and 79 ng/dL,

respectively. The mean average serum DHT concentrations for T-II and 2T-II were within the normal range.

The means of the averaged serum free testosterone concentration values at Hours 0 and 24 for placebo, Testoderm , T T-II and 2 x T-II were 3.8, 10.0, 10.8, and 17.1 pg/mL, respectively. The mean serum free testosterone concentration values at Hour 4 for placebo, Testoderm , T-II and 2T-II were 3.3, 14.1, 18.4, and 28.9 pg/mL, respectively. Free testosterone was elevated into the normal range for all active treatments. Serum free testosterone (FT) concentrations were above the assay limit of quantification in all of the three active transdermal testosterone treatment samples. The sponsor notes that approximately 30% of the baseline serum FT concentrations were below the assay limit of quantification.

The means of the averaged serum estradiol (E_2) concentration values at Hours 0 and 24 for placebo, Testoderm , T-II and 2 x T-II were 13.6, 14.7, 21.4, and 27.6 pg/mL, respectively. The mean serum E_2 concentration values at Hour 4 for placebo, Testoderm , T-II and 2T-II 11, 12, 21, and 29 pg/mL, respectively. Estradiol concentrations were in the normal range for men after all treatments. Serum estradiol (E_2) concentrations were above the assay limit of quantification in most samples from the four treatment groups. The sponsor states that about 5% of the serum E_2 concentrations were below the assay limit of quantification, and about 16% of the sample concentrations were not run because of insufficient quantities of serum.

The ratio of testosterone to Dihydrotestosterone was evaluated to determine if this was maintained within the physiologic range unlike the scrotal system. The ratios with the scrotal transdermal system are significantly altered because of the high metabolism through the skin of testosterone to DHT. The mean serum concentration ratios of testosterone to DHT for placebo, T-II and 2T-II and Testoderm treatments were 9.5, 7.6, 8.2, and 1.8, respectively. The ratios for placebo, T-II and 2T-II were statistically significantly larger than those of Testoderm treatments. The ratios were not statistically significantly different among placebo, Testoderm -II, and 2 x Testoderm -II treatments, suggesting that there was no appreciable skin metabolism of drug.

The sponsor estimated that using Testoderm as the reference, the amount of testosterone delivered following Testoderm-II application was nominally 6 mg, based on the baseline corrected AUC ratio. (see the pharmacokinetic review)

The following table is from the sponsor's submission.

Summary of Estimated Mean Pharmacokinetic Parameters for Serum Testosterone Concentrations (n = 19) Study 044

Parameters	Placebo	Testoderm (60 cm^2)	Testoderm-II (60 cm^2)	2 x Testoderm-II (2 x 60 cm^2)
C_{max} [ng/dL]	157	403	570	941
$^{*}T_{max}$ [h]	13.0	3.0	3.0	3.0
C_{min} [ng/dL]	51	161	201	326
$^{*}T_{min}$ [h]	4.0	13.1	0.0	0.0
k [h^{-1}]	N/A	0.68	0.74	0.50
$t_{1/2}$ [h]	N/A	1.79	1.62	1.75
$AUC_{(0-24)}$ [ng·h/dL]	2,302	6,179	9,378	14,003
C_{avg} [ng/dL]	96	257	391	583
$^{+}DAUC_{(0-24)}$ [ng·h/dL]	-	3,877	7,075	11,700
$^{+}DC_{avg}$ [ng/dL]	-	162	295	488

* *Median Value* $^{+}$ *Difference from placebo PK Parameters - table from sponsor*

The data submitted by the sponsor suggests appropriate delivery of adequate amounts of testosterone as demonstrated with each of the pharmacokinetic parameters. The sponsor believes that the serum testosterone concentrations were dose proportional to the surface area of Testoderm-II

Three patients in this study had inadequate serum concentrations of testosterone with the single Testoderm patch. Importantly, all of these patients had adequate amounts of testosterone with two patches. Four

patients had testosterone levels ≥ 1000 ng/dL at 3 hours with two patches. These patients are identified in the following table.

Serum Concentrations ng/dL

Patient	Testoderm-II	2 x Testoderm-II
	225	355
	160	584
	238	395

The 30 systems worn by the 19 patients were analyzed for residual testosterone content to determine the amount of testosterone delivered from the system. The sponsor states that he mean dose of testosterone delivered from one Testoderm-II system was 3.3 mg.

The adhesion rate in this study was excellent. Eighty-eight (77.9%) of the systems had a perfect adhesion score and 25 (22.1 %) had an adhesion score of 1 or less. Detachments occurred in 0.3% a in this study. Supplemental tape was used in 54% of the systems. No systems needed to be reapplied.

8.1.4.3 Safety comparisons

The post-treatment skin site assessment results indicated that all three active testosterone treatments were well tolerated. The only adverse events considered to be probably related to treatment were topical skin reactions that included: mild erythema that lasted between 2 and 6 days in one patient (5%) after Testoderm -II (one patch) treatment, mild erythema in three patients (16%) after T-II (2 patches) treatment, and mild to moderate itching in two patients (11%) after T-II (2 patches) treatment. Patient reported persistent and bothersome moderate itching on Days 6 and 7 of the Testoderm-II (2 patches) treatment. Patient reported occasional moderate itching on Days 4 and 5 of the Testoderm-II (2 patches) treatment.

After the removal of the Testoderm -II system removal on Day 7, no patients had definite redness at any time. At 24-hours post-system removal, 95% of patients had no redness, and 5% had barely perceptible redness. On Day 8 after removal of the Testoderm -II system, barely perceptible redness was reported in three patients at the 1-hour assessment (Patients).

All three treatments were well tolerated. Topical effects were evaluated at the system application skin site at 1, 6, and 24 hours after removal of the Day 6 system (assessment made on Day 7 of the two Testoderm -II treatments only) and after removal of the Day 7 system

(on Day 8 of all three active treatments). On Day 8, no topical skin reactions were reported for the scrotal Testoderm treatment.

After removal of the Testoderm-II (2 patches) systems on Day 7, definite redness was reported in Patient at the 1-hour assessment, in two patients at the 6-hour assessment (Patients , and in two patients at the 24-hour assessment (Patients After removal of the 2 x Testoderm-II treatment systems on Day 8, only barely perceptible redness was reported in six patients at the 1-hour assessment (Patients , in four patients at the 6-hour assessment (Patients and in Patient at the 24-hour assessment.

After removal of the Testoderm-II system on Day 7, mild itching was reported by Patient at the 1-hour assessment. On Day 8, mild itching was reported in Patient at the 6-hour assessment after Testoderm-II system removal. After removal of the Testoderm-II (2 patches) on Day 7, mild or moderate itching was reported at the 1-hour assessment by five patients (Patients , by two patients at the 6-hour assessment (Patients and by two patients at the 24-hour assessment (Patients

On Day 8 after removal of the 2 x Testoderm-II system, edema at the treatment site was reported in Patient

Testoderm-II

	Erythema	Extent of Erythema	itching
1 patient (5%)	none	mild - 2 - 6 days	none
3 patients (16%)	none	mild	none
2 patients (11%)	none	none	mild to moderate

There were no other safety issues.

8.1.5 Reviewer's Comments

The sponsor has demonstrated that the testosterone delivered with the new transdermal system was within the normal physiological levels. Although three of the nineteen patients had inadequate delivery with a single patch the addition of a second patch brought the testosterone levels within normal boundaries. In addition, unlike the scrotal patch there does not appear to be the first pass metabolism of testosterone to dihydrotestosterone since the normal physiological

ratios of T to DHT are maintained. There does not appear to be any increased aromatization of T to estrogen. The patch appeared to adhere satisfactory to the skin.

Three patients terminated prematurely. All were on placebo. (patients and all withdrew due to vascular access problems.

8.2 Trial # C-95-045

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8.2.1 Objectives

The objectives of the second pivotal trial stated by the sponsor were:

- to provide the pharmacokinetics of testosterone concentration delivered on the 1st and 5th day of application (upper buttocks);

- determine the 24-hour pharmacokinetics of serum testosterone concentration resulting from application of Testoderm-II to the back, upper buttocks, or upper arm;

- compare testosterone serum concentrations with and without Testoderm-II application; and

- evaluate topical safety.

8.2.2 Design

This study had four treatments designed to determine the pharmacokinetic parameters of serum testosterone concentrations after application of Testoderm-II transdermal system to the back, upper arm, and upper buttocks of 13 hypogonadal male patients. In addition, the pharmacokinetics of testosterone delivered by single

dose and steady-state dosage Testoderm-II were determined. Dihydrotestosterone (DHT), estradiol (E_2), and free testosterone (FT) concentrations were also determined at 0, 4, and 24 hours for each treatment. Each Testoderm-II, 60 cm^2 contained 328 mg testosterone, nominal delivery of 4-7 mg/day.

8.2.3 Protocol

8.2.3.1 Population, procedures

Of the 14 patients enrolled in the study, 13 completed the study. Patient withdrew on Day 1 because of elevated blood pressure.

8.2.3.2 Endpoints

Inclusion and exclusion criteria are the same as the first pivotal study (see page B-5). The following treatments included:

Treatment A: baseline without any system application with blood sampling done periodically for the entire 24 hours of the first day of the study;

Treatment B: Testoderm-II 60 cm^2, containing 15 mg testosterone with a nominal delivery of 6 mg/day applied to the upper buttocks and worn 24 hours. After a 2-day drug washout, daily applications were repeated for 5 days;

Treatment C: Testoderm -II 60 cm^2 applied to the upper arm and worn 24 hours; and

Treatment D: Testoderm-II applied to the back and worn 24 hours.

The sponsor generated a randomized assignment schedule, and each patient was assigned to one of the following treatment sequences.

Sequence 1: **A, B, C, D**
Sequence 2: **A, C, D, B**
Sequence 3: **A, D, B , C**
Sequence 4: **A, B, D, C**
Sequence 5: **A, C, B, D**
Sequence 6: **A, D, C, B**

Blood samples were drawn to determine serum testosterone (T), dihydrotestosterone (DHT), estradiol (E_2), and free testosterone (FT) concentrations; testosterone pharmacokinetic parameters ($AUC_{(0-27)}$, $AUC_{(0-24)}$, C_{max}, T_{max}, C_{avg}, C_{min}, T_{min}, k, and $t_{1/2}$) were estimated. Adhesion was assessed at the time of system removal. Skin sites were assessed for evidence of topical effects at 1, 6, and 24 hours after system removal.

A total of 68 blood samples were drawn from each patient. An additional 50 mL was required for pre-and post-study laboratory tests. Blood for serum testosterone and dihydrotestosterone, and for estradiol and free testosterone assays as collected at 0, 4, and 24 hours post application during the pharmacokinetic profiles for Treatment A and Day 7-8 of Treatment B.

Serum testosterone, dihydrotestosterone, estradiol, and free testosterone concentrations were measured using [redacted] as in the previous protocol.

8.2.3.3 Statistical considerations - see statistical review

The sponsor states the following: The single dose pharmacokinetic parameters $AUC_{(0-27)}$ and C_{max} were examined using the analysis of variance (ANOVA) method after log transformation using PROC GLM (PC SAS, version 6.10). The variance model consists of the sequence, patient within sequence, treatment times sequence, and treatment effect. For each paired treatment comparison, the 90% confidence interval of the mean ratio was constructed using the residual error from the ANOVA model.

For the upper buttocks application, the $AUC_{(0-24)}$ of the first and the fifth doses after log transformation were compared using PROC GLM (PC SAS, version 6.10) to assess the drug accumulation. For the upper buttocks application, the $AUC_{(0-24)}$ of the first dose was compared with the steady-state $AUC_{(0-24)}$ after removing the carryover effect from the fourth dose after log transformation using PROC GLM (PC SAS, version 6.10) to assess the time-invariance of testosterone kinetics.

8.2.4 Results

8.2.4.1 Patient Disposition

All 14 patients in this study were hypogonadal males and ranged in age from years old; 9 were Caucasian, 4 were Black, and 1 was Hispanic. Mean demographics are summarized in the following table from the sponsor.

Summary of Patient Demographics

Baseline Variable	Enrolled (n=14)	Completed (n=13)
Age (Years)		
Mean ± SD	**48 ± 12.5**	**49 ± 12.7**
(Min, Max)		
Sex		
Male	**14 (100%)**	**13 (100%)**
Ethnic Origin		
Black	**4 (28.6%)**	**3 (23.1%)**
Caucasian	**9 (64.3%)**	**9 (69.2%)**
Hispanic	**1 (7.1%)**	**1 (7.7%)**
Height (cm)		
Mean ± SD	**177 ± 8.1**	**178 ± 5.8**
(Min, Max)		
Weight (Kg)		
Mean ± SD	**92 ± 7.8**	**91 ± 8.0**
(Min, Max)		

From Sponsor's table

8.2.4.2 Efficacy endpoint outcomes

During the 24-hour baseline period the sponsor states that approximately 10% of serum testosterone concentrations were less than the assay limit of quantification; the average serum testosterone concentration, C_{avg}, for this baseline period was 176 ng/dL. Serum testosterone concentrations were greater than the assay limit of quantification in all but 5 of the 546 samples from the three of the Testoderm-II 24-hour treatments. In most patients, serum testosterone concentrations increased about ng/dL above baseline after Testoderm-II treatment; mean serum testosterone concentrations were maintained within the normal range from Hour 2 to Hour 24 (system removal) for all Testoderm-II treatments: 337 (Hour 2) to 348 ng/dL (Hour 24) for the upper buttocks application, 350 (Hour 2) to 319 ng/dL (Hour 24) for the upper arm application, and 413 (Hour 2) to 321 ng/dL (Hour 24) for the application to the back (Table 1, Figure 1). All Testoderm-II treatments produced an early increase in serum testosterone concentrations as the median T_{max} value was about 4 hours after system application. The mean serum testosterone concentration-time profiles were similar after each of the four Testoderm-II treatments.

Mean C_{max} values after each of the Testoderm-II treatments were more than twice the mean baseline value of 229 ng/dL: 482 ng/dL for the upper buttocks application, 462 ng/dL for the upper arm application, and 499 ng/dL for the application to the back. The following table summarizes the estimated mean pharmacokinetic parameters for the serum testosterone concentrations after application at each of the three sites. The estimated mean pharmacokinetic parameters for Testoderm-II applied to upper buttocks on Day 5 were similar to those on Day 1.

The table on the following page from the sponsor gives a summary of the estimated mean pharmacokinetic parameters after the application of Testoderm-II to three different sites.

Summary of Estimated Mean Pharmacokinetic Parameters for Serum Testosterone Concentrations After Application of Testoderm-II to Three Different Sites (n = 13) Study 045

Parameters	Baseline (A)	Treatments: Testoderm-II Upper Buttocks (Day 1) (B)	Testoderm-II Upper Arm (Day 1) (C)	Testoderm-II Back (Day 1) (D)
C_{max} (ng/dL)	229	482	462	499
$^{\cdot}T_{max}$ (h)	4.0	3.9	4.0	3.9
C_{min} (ng/dL)	129	164	135	156
$^{\cdot}T_{min}$ (h)	17.0	0.0	0.0	0.0
k (h^{-1})	N/A	0.52	0.52	0.57
$t_{1/2}$ (h)	N/A	3.3	2.1	2.7
$AUC_{(0-27)}$ (ng·h/dL)	4,752	9,560	8,651	8,988
C_{avg} (ng/dL)	176	N/A	N/A	N/A
$^{+}DAUC_{(0-27)}$ (ng·h/dL)	-	4,808	3,899	4,236

$^{\cdot}$Median value $^{+}$Difference from baseline pharmacokinetic parameters- table from sponsor

The sponsor states that the results indicated that there were no statistically significant differences among log transformed testosterone pharmacokinetic parameters ($AUC_{(0-27)}$, C_{max}, T_{max}, $DAUC_{(0-27)}$) after application of Testoderm-II to three different sites.

The means of the averaged serum free testosterone concentration values of Hours 0 and 24 for baseline and Testoderm-II Day 5 treatment were 8.8 and 14.0 pg/mL, respectively; the mean Day 5 values were within the normal range. The mean serum FT concentrations at Hour 4 were 7.9 pg/mL during baseline and 22.4 pg/mL on Day 5 .

The means of the averaged serum E_2 concentration values of Hours 0 and 24 for baseline and Testoderm-II Day 5 treatment were 17.2 and 22.9 pg/mL, respectively; the mean Day 5 values were within the normal range. The mean serum E_2 concentrations at Hour 4 were 17.1 pg/mL during baseline and 24.1 pg/mL on Day 5 .

8.2.4.3 Safety comparisons

No topical effects were reported at any application site in this study. The same rating scales were used as in the previous protocol. See page B-6

Adhesion rates were also excellent in this study. In study 045 Twenty one per cent of the applications were taped by the patient. 90% of the applications had an adhesion score of 0 and 1. One system came off during the applications.

Patients excluded from analysis -

One patient withdrew on Day 1 of the baseline period and no pharmacokinetic data were obtained. He received no active treatments.

8.2.5 Reviewer's Comments:

Sponsor's Statements:

"There were no statistically significant differences between log transformed testosterone $AUC_{(0-24)}$ after application of Testoderm-II to upper buttocks on Day 1 and Day 5. The accumulation ratio of the fifth dose to the first dose was 0.91. This demonstrated that there was no appreciable accumulation nor changes in drug metabolism.

Of the 14 patients enrolled in this study, 6 patients reported at least one adverse event; no single adverse event was reported by more than one patient. All adverse events were categorized by the investigator as definitely not related to treatment.

One patient had mild to moderate elevations in blood pressure during the study due to his underlying hypertension. No other clinically significant changes in vital signs were noted by the investigators for any patient during this study.

At the assessment 24 hours after removal of Testoderm®-II worn on Day 1 or Day 5, no topical effects were reported at any application site."

The reviewer finds no discrepancies with the statements provided by the sponsors. All of the application sites appeared to provide adequate and clinically relevant amounts of testosterone. There was no evidence of increased metabolism of testosterone to dihydrotestosterone.

The safety profile of this system appears excellent. There was no evidence of skin irritation. The adherence rate has not been provided. but is assumed to be excellent because of the identified testosterone delivery.

8.3 Supporting Studies:

The sponsor has provided data on 6 supporting studies. These include two comparator trials to the approved non-scrotal system, Androderm, as well as additional topical safety trials.

8.3.1

C-96-025	Contact sensitization study n=233	Testoderm II - 6 mg 1 patch

This was a standard topical safety and sensitization study done in normal men which included a population of elderly men (≥65 years of age). The elderly study was done in A total of 207 patients have completed the entire trial. Eighty Five elderly men have been enrolled in and 80 have completed this study.

In this protocol each man had 2 non-scrotal patches (Testosderm II) applied to the back for 48 hours. The patches were then removed and the skin examined for any sign of contact sensitization. This application was repeated 9 times over approximately a 3 week period of time. Following a two week rest period two additional challenge applications of 24 hours each were applied. In this study thirty-five percent of the population were ≥65 years of age. The study was in two phases. The first was induction and challenge . In the induction phase each subject received 9 open-label applications of a 60 cm^2 system in a 24 - day period. Three applications per week which were applied to rotated sites. . After a 14 day rest period without any systems subjects entered the challenge phase. Each double-blind challenge application comprised one Testoderm-II system and one placebo system .

Contact sensitization was defined as a site that demonstrated persistent redness with sudden induration that was palpable associated with pruritus. The sponsor notes that the contact sensitization rate during the challenge phase of this study was 0.5% representing one 42 year old subject who demonstrated contact sensitization with his first challenge application.

Sixty nine percent of the subjects in this study had no adverse events; however, in this study there were four cardiovascular events. These

have been previously reviewed and do not appear to be drug related. All of the patients had pre-existing hypertension and may have been obese. Two of the men had myocardial infarction and one man died.

- A 65 year old with a history of hypertension experienced chest pain with the first application of the patch . The time of the event was not clear but may have been approximately 8 - 10 hours after start of patch. He went to the hospital were he had an angioplasty. (Patient

- A 71 year old experienced a myocardial infarction (MI) the last day of August. He was in the rest period between the completion of the first 3 weeks and the rechallenge. He complained of congestion and was treated with antibiotics first, for the shortness of breath and diarrhea, and finally diagnosed with an MI. (Patient

- A 65 year old patient fell and presumably fractured his femur on 9/7/96 . While he was in surgery for the repair he suffered a heart attack and died. It was thought that the stress of surgery precipitated the event. The patient also had a history of hypertension. He was not on the active patch at the time but was in the rest period. (Patient

- A 69 year old male who had completed the first portion of the protocol, was receiving a testosterone challenge on September 12 and experienced fatigue. He was taken by ambulance to the hospital were he was diagnosed with 'water around heart'. The diagnosis is not final but presumably he had either an MI or a pericardial infusion. He also had a history of hypertension. (Patient

It is unlikely that these events are related to the testosterone patches. The reports would suggest that each of these men was obese. None of the men appeared to be within 10% of normal body weight.

8.3.2

C-96-026-03	21 days/28 n=29	Topical safety of Testoderm

This was a study designed to assess the incidence of phototoxicity and the photocontact allergencity potential of the system . Each subject received 8 Testoderm-II systems over a 6 week period. Each system was applied for 24 hours. The study included an induction phase and a challenge phase. To test for phototoxicity after removal of each system the skin sites were evaluated for evidence of local reactions and then exposed to visible and long-range ultraviolet light at 15 Joules/cm2 of ultraviolet-A light.

A total of 29 patients were enrolled in this study. Two subjects terminated prior to completion and were replaced. One was due to job complications and one to an adverse event. Subject had a skin reaction at the site of the application with erythema of 3+. The patient is thought to have had a positive allergic response to topical testing with ethanol. One patient had a preexisting malignant skin lesion. There is no evidence provided that any of the patients had demonstrated phototoxicity.

8.3.3

C-96-005-022	28 days/70	Androderm 5.0 mg* Testoderm-II 6 mg

The primary objective of this study was to assess the cumulative erythema rate of Androderm and compare it to that of Testoderm-II. The efficacy measurements to be collected were:

- severity of erythema , papules and allergic reactions.
- patient preference for the two testosterone transdermal systems;
- conditions under which systems love adhesion'
- patient preference for site of application;
- serum testosterone concentrations.

76 patients were enrolled at 8 study sites. 70 patients completed the study. Investigators: Clark, Cook, Dobs, Duckett, Katznelson, Kipnes, Mooradian, and Snyder. This was an open label, randomized, two sequence, two -treatment, two period, crossover study. Patients were randomized equally into one of two treatment sequences. 39 patients were randomized to Testoderm first and 37 to Androderm first. Each treatment was 28 days. At the end of the study patients were asked to rank their preference for each system.

Blood samples were collected at baseline and on days 14 and 28 of each of the two treatment periods. All blood sampling was obtained on a biweekly basis 3 - 5 hours after the application of the Testoderm-II system or 8 - 12 hours after application of the Androderm system.

The mean serum testosterone concentrations would suggest that Androderm delivery was slightly superior although in most cases these were all within clinical boundaries. The mean serum testosterone concentrations of each treatment at 2 and 4 weeks are noted in these next table.

Testosterone Delivery
005

	Baseline n=76	Testoderm 2 weeks n=74	Testoderm 4 weeks n=65	Androderm 2 weeks n=75	Androderm 4 weeks n=64
Mean T	224.79	358.96	377.93	461.17	424.96

Three of the patients in this study had increases in hematocrit above the normal range. These were patients . Patient had an increase in hematocrit from 47& at baseline to 55% and an increase in hemoglobin from g/dL g/dL. His medical history also included emphysema.

The skin irritation profile was clearly superior for the Testoderm system and agrees with the sponsor's statement that the data indicates that the incidence of topical events is lower for Testoderm than for Androderm.

Skin Irritation
005

Topical event	Testoderm-II	Androderm	*p value*
Erythema	6.7%	26.7%	*0.001*
Edema	2.7%	10.7%	*0.058*
Papules	1.3%	5.3%	-
Itching	5.3%	6.7%	-

In this 56 day study the sponsor has demonstrated the comparability of their product, Testoderm-II, to Androderm, the approved transdermal testosterone system. Although the Alza product appears to deliver slightly lower amounts of testosterone it is within clinical boundaries in most cases and the safety profile appears more satisfactory than that of Androderm. Seven patients discontinued the study; five of these patient discontinued due to adverse events. Five of the seven patients who discontinued were due to adverse events. Two of the patients discontinued while receiving the Androderm system due to skin irritations, e.g. pustules and open sores, at the site of the system application. The patient who discontinued the Testoderm system did so because of a mild to moderate generalized rash with pruritus.

The sponsor notes that patients indicated that they felt Androderm was a better treatment than Testoderm in terms of effectiveness, side effects, convenience, and wearing comfort. The same patients indicated a preferred application site as the lower back. The sponsor believes that these data indicate that the incidence of topical events is lower for Testoderm - II than for Androderm treatment.

8.3.4

C-96-022-03	14 days/25	Androderm 2.5 Testoderm II 6 mg

This study was in two parts and was done to compare the approved Androderm system to the Testoderm system. Part 1 studied the cumulative irritation of the Testoderm-II applied 10 times to the same skin site over 14 days. The same skin irritation parameters were used as for all previous studies. The results suggested that repeated application of the system resulted in negligible skin irritation in 81% of subjects. Nineteen percent of the subjects had occasional skin assessment scores of 2 (definite redness).

Part 2 of this study compared Androderm and Testoderm-II applied simultaneously each day for 14 days to rotating skin sites on the back. 33 volunteers participated in this study. Each subject received 14 systems (either Androderm and Testoderm) during the 2 week period. Topical effects were evaluated as previously.

Three of 33 subjects reported itching, one each reported acne and pruritus. It does not appear that any superiority claims can be made from this study.

8.3.5

C-96-048-01	4 days/8 patients	Testoderm-II* pharmacokinetics

This was a short open label study to the steady-state serum testosterone pharmacokinetic parameters of an artificially elevated release-rate Testoderm-II system in order to define the clinical relevance of the upper boundary of the in vitro release rate specification. The study included 8 hypogonadal men with testosterone concentrations not exceeding ng/dL. Each patient wore one elevated release rate testosterone transdermal system each day for 4 consecutive days. Each system had a nominal delivery of 6 mg of testosterone per day for a total of 24 mg per patient during the study.

Two of the subjects had adverse events. one with skin reactions at three system application sites which responded to hydrocortisone cream. The second patient had a moderated headache.

The C_{avg} (391 ng/dL) and C_{max} (570 ng/dl) for the elevated release rate system were similar to those in study 95-044 and the systems were well tolerated.

8.3.6 -

C-96-079	5 days/21 patients	Testoderm-II

An additional study .C-96-079-01, was an evaluation of adhesion, placement and topical skin effects of Testoderm-II under stress conditions, e.g. perspiring and active. The study was designed to evaluated adhesion rates and acceptability of reapplication of detached systems.

Twenty-one patients applied one system daily for five days to each of the three sites, e.g. upper buttocks, mid or upper back, and arm. The subjects completed a daily diary and recorded the number of times a system fell off and the activities associated with the events. The patients did not use any supplemental tape.

There were 314 applications and 154 became detached one or more times during a 24 hour period especially during bathing or showering. 51% of the patches never fell off during the 24 hour wearing period. The study supports the label suggestion that patients may want to temporarily remove the system before swimming, bathing or heavy exercise and afterwards reapply it to dry clean skin.

9 Overview of Efficacy

The following table notes the comparative androgen results between the different delivery systems from the submitted studies.

Mean at 4 hours for Testosterone - Testoderm Systems

System	Testosterone ng/dL	DHT ng/dL	FT pg/mL
Study	044/045	044/045	044/045
1 - Testoderm-II	468/382	47/52	18.4/22.4
2 - Testoderm-II	766/ -	79/-	28.9/-
Scrotal T	342	146	14.1
Baseline	82/187	9/20	3.3

N=19 study 044; N= 13 study 045

The adhesion rate of any transdermal system is important for the appropriate delivery of testosterone. Transdermal systems inherently may have difficulties especially with exercise. Adhesion ability may be related to the skin, temperature and activities of the patients. The use of supplemental tape may be necessary for some to maintain skin contact. In all of the studies only two patients discontinued because of adhesion difficulties. In a total of 490 systems applied in studies 044 and 045 detachments or fall-offs occurred in only 0.4% of the systems (0.3% in study 044 and 1.1% in study 045). . Partial lifting (less than 75% contact with skin) was reported in 3 of the 490 systems. In the pivotal trials no patients discontinued because of adhesion difficulties. Study 079 evaluated more fully the acceptability of the system with stress and reapplication. Those patients with problems could add adhesive to the system.

10 Overview of Safety

The safety profile and in particular the skin irritation scores looked remarkable well for the pivotal studies, 044 and 045, even they were short in duration. The studies longer in duration, e.g. 026 and 005, did not demonstrate any increased skin irritation profile.

Study 96-005-02 was a comparison study of the wearing acceptability of two testosterone transdermal systems. There were a total of 76 men enrolled in this study . It was a multicenter study with an open-label randomized, two -period crossover of two transdermal testosterone treatments. comparing Testoderm-II and Androderm. The following table notes the skin assessment scores.
In Study 025-04 the contact sensitization rate was 0.5% representing one subject who demonstrated a contact sensitization with his first challenge application. The erythema rate was highest immediately after system removal (5.9%) and decreased to 3.3% at 72 hours after system removal. One subject was discontinued from the induction phase due to scores of 3 with papules and pustules 48 to 72 hours after system removal for two consecutive applications. There were in this study application site reactions which included itching in 17.2% of subjects and erythema in 2.6% of subjects. Other skin changes were notes in <1% of subjects.

In 026-03 after ten repeated applications of Testoderm-II over 14 days to the same skin site there were negligible skin irritation noted in 81% of the subjects. Nineteen percent of subjects had occasional skin assessment scores of 2 (moderately intense erythema)

% irritation	Testoderm Scrotal Patch* 2%	Androderm Nonscrotal*	Testoderm-II - AT
Itching	7%	-	
Erythema	-	7%	-
Pruritus at site	-	37%	-
Burn-like Blister	-	12%	-

* from label

The known risks of androgen therapy include adverse changes in the lipid, hepatic and red cell mass profile. No consistent changes in the lipid or hepatic profile were noted. Three patients in study 005 had changes in erythrocytosis. The normal range in males is 38-45% hematocrit. 50% or greater hematocrit has been associated with increased blood viscosity and possible thrombosis. The label notes

,under Laboratory Tests, the importance of periodic evaluation of hemoglobin and hematocrit levels.

The Annual Report of June 19, 1997 includes the safety summary of the 8 clinical studies from Alza. The table below notes that there are little changes in skin irritation between the update and the NDA.

Skin	NDA	ISS + update
site itching	55 (12.6%)	55 (12%)
site erythema	15 (3.4%	15 (3%
Pruritus	7 (1.6%	7 (1.5%)
burning	4 (0.9%)	5 (1.1%)
rash	5 (1.1%)	5 (1.1%)
papules/pustules	4 (0.9%)	4 (0.9%)
vesicles	2 (0.5%)	2 (0.4%)

11 **Labeling Review**

There are no changes recommended in the label. The label follows the format of the Androgen Class Label and the previously approved Testoderm scrotal system. It accurately notes the data from the clinical trials.

The label should note the percentage of men who used adhesive and percentage of detachments of systems during exercise. It is acceptable to state that the system can be removed and replaced after swimming etc. (study 079).

The only new addition to the label is the discussion of sleep apnea and testosterone esters. Although sleep apnea has been associated with testosterone replacement, this association has been with concomitant risk factors ,e.g. obesity or chronic lung diseases. The addition of this component to the label is acceptable.

The patient instructions for use are acceptable and similar to the previously approved PPI.

12 Conclusions

This new non-scrotal transdermal system is approvable.

13 Recommendations

The only suggested label change is a better description of the adhesion rate.

Jean L. Fourcroy, M.D., PhD
Medical Officer
HFD-580/JFourcroy/HJo' /25/97

NDA 20-791 **Amendment** dated October 24, 1997

NOV 26 1997

Medical Officer Review of Safety Update

Received: October 27, 1997
MOR complete: November 24, 1997

Sponsor: ALZA Corporation
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Drug: Testoderm® TTS (Testosterone Transdermal System)
Dosage: 6 mg/daily
Route of Administration: transdermal
Indication: Testosterone replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone.

Background: The purpose of this submission is to update the clinical activity with Testoderm ® TTS prior to the regulatory action date. This one volume submission contains the final report for Study #C-96-079, entitled "Evaluation of Adhesion, Placement and Topical Skin Effects of Testoderm ® -II". This study was initiated after the time of the original NDA submission on December 19, 1996. Also enclosed are brief updates on the following four studies using Testoderm ® TTS:

Final reports for 7 other studies (C-95-044, C-95-045, C-96-048, C-96-025, C-96-026 and C-96-022[parts 1 and 2]) were submitted in the original NDA 20-791 and are reviewed in the Medical Officer's Review of Testoderm-II .

Study #C-96-079

Summary of the Study Design: Study #C-96-079 was an open-label, three period, crossover design study, conducted in 20 healthy, male volunteers at a single investigative site. The objective of the study was to assess system adherence under "stress" conditions (e.g. perspiring, physical activity). Each patient received three treatments, in randomized sequence. Each treatment period consisted of 5 consecutive 24-hour applications of Testoderm-II, differing only by application site (upper buttocks, upper or mid back and upper arm) and separated by two-day washout periods. Adhesion quality, as measured by number of detached systems (systems "falling off") in a 24-hour wearing period, was assessed by patient diary. Application sites were assessed for skin irritation one hour after system removal on the sixth day of each treatment period.

The patient population included healthy males, 18 to 40 years of age, who agreed to use an effective birth control method during the study treatment period and for 1 month following the study and were actively engaged in any form of physical labor or activity for at least 4 hours during the day. Subject candidates with an active skin disease or a history of skin allergies or sensitivities were excluded.

Topical skin assessments were scored on a 0 to 3 scale as follows:

Score	Erythema	Extent of Erythema	Itching
0	none	None	None
1	barely perceptible redness	<50% occluded area	Mild
2	definite redness	>50% occluded area	Moderate
3	"beet" redness	Not applicable	Severe

Patient preference for application site (e.g. most comfortable, best adherence, overall preference) was assessed by patient questionnaire on the final day of the study.

Adverse event information was solicited by the investigator from the subject, graded for severity (mild, moderate or severe), assessed for causality, and recorded on an Adverse Event CRF at each assessment visit.

Results of the Study: Of 22 subjects enrolled in the study, 21 completed the entire study. Subject withdrew on Day 2 of the first treatment period because of an unrelated illness (influenza).

Adherence Data

Incidence of Detachment: In 21 evaluable patients, for the entire 15-day treatment period, 314 systems were applied and 154 systems **(49%)** fell off during a 24 hour wearing period. Seventy-seven systems (24.5%) fell off on a single occasion. Seventy-

seven systems (24.5%) fell off on more than one occasion. The 154 systems which fell off were successfully re-applied in 103 instances (67.8%).

Site of Application and Adherence: Rates of system detachment (where the system fell off on one or more occasions during a 24 hour wearing period) for upper buttocks, upper arm, mid-back and upper back were 40.9%, 46.8%, 48.6%, and 92%, respectively.

Activity and Adherence: Patients were asked to report the activity being performed when the system fell-off. The categories were: during exercise, during sleep, during showering/bathing, during work, as a result of perspiring, during other activities, and unknown. Patients could select more than one category for each detachment (fall-off). Detachment was reported during showering or bathing 73 times, during sleep 46 times, during exercise 41 times, as a result of perspiring 37 times, during other activities 29 times, during work 15 times and unknown 10 times.

Site of Application, Activity and Adherence: When applied to the upper back, upper buttocks, and upper arm, the activity most commonly reported during system detachment was showering/bathing (69.6%, 60.5%, and 47.1% of all reported activities, respectively). When applied to the mid back, the most commonly reported activity during system detachment was exercise.

Site Preference:

Most comfortable site of application: The most comfortable site of application was reported as upper buttocks by 13 subjects, upper arm by 5 subjects, mid-back by 3 subjects and upper back by 0 subjects.

Site of Best Adherence: The site of best adherence was reported as upper buttocks by 15 subjects, upper arm by 5 subjects, mid-back by 1 subject and upper back by 0 subjects.

Overall Preferred Site of Application: The site of overall preference was reported as upper buttocks by 14 subjects, upper arm by 6 subjects, mid-back by 1 subject and upper back by 0 subjects.

Skin Site Assessment:

Of the total 66 skin site assessments, **Grade 0 ("no erythema")** was noted on 62 occasions and **Grade 1 ("barely perceptible redness")** on 4 occasions. There were no Grade 2 or Grade 3 skin site assessments. There was one incident of mild itching and one incident of small papules.

Adverse Events:

Twenty-one (21) adverse events were reported in 16 subjects. No adverse event was rated as serious by the medical monitor. Headache was reported by 6 subjects, increased libido by 4 subjects, acne by 2 subjects, increased hair growth by 2 patients, increased energy level by 2 subjects, application site reaction by 2 subjects (mild tingling and mild

burning sensation at the skin site), cold/flu symptoms in 2 subjects and knee pain in 1 subject.

Reviewer Conclusions: These safety data reveal no serious medical events. The incidence and severity of topical effects are remarkably low for all sites and for all treatment periods. The reported adverse events are minor and consistent with the administration of exogenous testosterone to normal males (e.g. increased libido, acne, increased hair growth, increased energy level). These data support the safety profile of Testoderm-II in clinical studies.

In regard to the efficacy data, the reported incidence of system detachment in this study is markedly higher than that reported in the pivotal studies (0.3% in study 044 and 1.1% in study 045). Partial lifting (less than 75% contact with skin) was reported in only 3 of 490 systems in the two pivotal studies. The increased detachment rate in Study C-96-079 is likely due to increased perspiration with physical activity, longer daily duration of activity, more vigorous activity, and increased frequency of bathing/showering. Further, since the terms "detachment" and "fall-off" were incompletely defined in this protocol, such instances may actually represent lesser degrees of detachment, resulting in an overestimate of the "complete" detachment rate. The sponsor has accounted for these results in the **Dosage and Administration** section of the label and the **Patient Instructions Insert.**

In the **Dosage and Administration** section, TESTODERM® AT section, the sponsor notes,

In the **Patient Instructions Insert**, Item 7 describes in detail the procedure for temporarily removing your patch before swimming, bathing or heavy exercise.

The sponsor should include a better description of the adhesion rate in the label, specifically in the **Adverse Reactions** and **Dosage and Administration** sections. This description should account for the detachment rate in the pivotal studies as well as the higher detachment rate in study C-96-079.

Study C-97-014

This scope of this review is limited to the brief summary information presented in Attachment 3 of this submission and the protocol submitted under IND

Summary of the Study Design: This was a single center, open-label, randomized, two-treatment, two-sequence, crossover study. The primary objective of the study was to compare the incidence of skin site erythema obtained with Testoderm® TTS with that obtained with the commercially available Androderm® Testosterone Transdermal

system. The study consisted of two 14-day treatment periods, separated by a six-day washout period. Patients were randomly assigned to one of two treatment sequences; Androderm® followed by Testoderm® TTS or Testoderm® TTS followed by Androderm®. In each treatment period, one transdermal system was applied daily. Patients returned for daily office visits to remove and replace the system, rotate the site of application and assess the "just-removed" and 24-hour "post-removal" skin site. The skin site was scored on a zero (0) to four (4) erythema scale. The subject population was to include sixty healthy male volunteers, aged 18 to 65. Subjects 50 years of age or older were required to demonstrate a normal rectal exam and normal age-related PSA level. Subjects with partners of child-bearing potential had to agree to use an acceptable form of contraception for the duration of the study and for one month following the study. Subjects were required to refrain from using topical or systemic corticosteroids and could not have significant medical or dermatological conditions, a history of carcinoma of the prostate or BPH, or a history of breast carcinoma. A sample size of 60 was selected based on a presumed erythema incidence rate of 20% for Androderm®, a rate of 4% for Testoderm® TTS, an attrition rate of 10% and a presumed incidence of moderate to severe erythema in 2% of subjects for both treatments. That sample size should have provided 80% power to detect a 20% difference in the erythema incidence rate, using McNemar's test and a two sided α of 0.05.

Results of the Study: Sixty healthy male volunteers, aged 18 to 65 were enrolled in the study. Each subject completed 14 days of treatment with Testoderm® TTS and 14 days with Androderm® in a randomized, crossover design. A one-week washout period separated the two treatment periods for a total study duration of 37 days. The in-life phase of the clinical trial has "only recently been completed, and that data has not yet been collected nor analyzed".

Reviewer Conclusions: There are no safety data available for review in this study.

Dr. K. Sreekumaran Nair's Sponsor-Investigator Study # 547-96

This scope of this review is limited to the brief summary information presented in Attachment 4 of this submission and the protocol submitted under IND

Summary of the Study Design: This was an open-label, single center, multiple dose, parallel design study with the objective of comparing the topical irritation rates of Testoderm® TTS to Androderm® in elderly hypogonadal men. The design also included a pharmacokinetic assessment of serum testosterone levels during the first and last days of the 4 week study. Fourty (40), hypogonadal (serum testosterone <400 ng/dl), healthy male patients were randomly assigned to Androderm® or Testoderm® TTS. All subjects were admitted to a research center on day 1 , where blood samples were drawn every 10 minutes from 7 A.M. to 8 A.M., then every 2 hours for 24 hours. Subjects then wore one

Testoderm® TTS system or one Androderm® transdermal testosterone system daily for 4 weeks. Skin site assessment and random serum testosterone testing was performed on a weekly basis. At the end of the four week study period, all subjects were re-admitted to the research center where blood samples were drawn every two hours for 24 hours. Blood samples were measured for total and free testosterone and dihydrotestosterone levels. Skin site erythema and inflammation was scored on a zero (0) to four (4) scale. All patients underwent PSA testing and digital rectal exam (DRE) prior to randomization. Abnormalities of prostate on DRE were evaluated by prostate ultrasound with transrectal biopsy to exclude carcinoma of the prostate. Patients with ischemic heart disease, active angina pectoris, previous episodes of congestive heart failure, past or current history of prostate cancer or BPH, current history of any other malignancies, presence of erythrocytosis, liver dysfunction, electrolyte imbalance or renal insufficiency were excluded. The primary endpoint in this protocol was the patient discontinuation rate. Assuming a discontinuation rate of 5% in the Testoderm® TTS group (secondary to persistent skin irritation) and a 35% discontinuation rate in the Androderm® group, a sample size of 40 provides 90% power at the $\alpha = 0.05$ significance level to detect an 11% difference in the discontinuation rate.

Results of the Study: Fourty (40), healthy, elderly male subjects (≥60 years of age) enrolled in the study. One subject discontinued Testoderm® TTS prematurely due to worsening of angina pectoris which he had not reported prior to randomization. The sponsor reports, " Two (2) subjects reported mild itching, two (2) reported erythema lasting one to three days, one subject reported fatigue for one day, and muscle pain in the legs for two days." No further information was provided by the sponsor. The data from this study have not yet been analyzed nor reported.

Reviewer Conclusions: The safety data provided for this study are too limited to draw any major conclusions. However, the fact that 19 of 20 elderly, hypogonadal males successfully completed the entire study on Testoderm® TTS, with the rare appearance of adverse events, adds some support to the safety profile of this product in this age group.

Dr. Christina Wang's sponsor-investigator study, conducted under IND

Reviewer Comment: In Attachment 5, the sponsor notes that this study has not been initiated at the time of the safety update. Accordingly, the study is not reviewed in this safety update.

Dr. Eberhard Nieschlag's study at the Institute of Reproductive Medicine, University of Munster, Munster, Germany

Reviewer Comment: In Attachment 6, the sponsor notes that this study was initiated in 1996. Twelve healthy volunteers were to receive 500 μg of levonorgestrel and a single Testoderm® TTS system once daily, continuously over 24 weeks. Subjects were to visit

the clinic every three weeks. The objective of this study was to determine if a combination of levonorgestrel and Testoderm® TTS would be a useful approach to male contraception. Unfortunately, as noted by the sponsor, "Enrollment, discontinuation and safety data have not yet been reported by the investigator". Since there are no results reported, this study is not reviewed in this safety update.

Summary: The results of these studies, particularly Study C-96-079, support the safety of Testoderm® TTS. The local topical inflammatory reaction appears limited and mild. There are no additional systemic nor local adverse events reported in this safety update.

The increased rate of system detachment reported in Study C-96-079 demonstrate that system adherence is considerably less adequate in situations "of stress", such as exercise, bathing, showering, or perspiring.

The sponsor has addressed this issue of system adherence in the **Dosage and Administration** section with two sentences as follows:

Additional information is provided to the patient in the **Patient Instructions Insert** under Item 7. The sponsor should include a better description of the adhesion rate in the label, specifically in the **Adverse Reactions** and **Dosage and Administration** sections. This description should account for the detachment rate in the pivotal studies as well as the higher detachment rate in study C-96-079.

Recommended regulatory action: In summary, this safety update supports the safety profile of Testoderm® TTS. The submitted data do not reveal any significant changes in the safety profile of Testoderm® TTS from previous clinical study reports. In regard to the increased rate of system detachment reported under "conditions of stress", the following recommendations are made:

These recommendations should be conveyed to the sponsor in the information request letter which summarizes all other recommended label changes.

Mark S. Hirsch, M.D.
Medical Officer
HFD-580
cc:
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11/26/97