CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

MEDICAL REVIEW(S)

Date NDA Submitted:	**December 31, 2001**
Date NDA Received:	**December 31, 2001**
Review Completed:	**October 21, 2002**
Review Finalized:	**October 30, 2002**
	Medical Officer's Original Review
Sponsor:	**Auxilium Pharmaceuticals Inc.** **160 West Germantown Pike** **Norristown, PA 19401**
Drug Name:	**Generic:** testosterone gel **Trade:** Testim™ 1% (testosterone gel) **Chemical:** 17β-hydroxyandrost-4-en-3-one
Pharmacologic category:	androgen steroid
Route of Administration:	transdermal
Dosage Form:	gel
Strength:	50 mg and 100 mg (1% testosterone)
Proposed Indications:	testosterone replacement therapy in [redacted]
Related Submission:	IND 61,307 for the same indication
Related documents:	Major amendments received: safety updates on 5-06-02 and 7-03-02 Minutes of meetings: see section I. Regulatory History of review

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The Executive Summary of the Primary Clinical Review

1. RECOMMENDATIONS

1.1 Recommendations on Approvability

The reviewer recommends approval of Testim™ as presented in NDA 21-454 and the associated safety updates. There were no major efficacy issues. The sponsor wanted to establish a claim for

The safety issue of potential transfer of drug by direct skin contact with another person [especially women and children] was resolved by more detailed assessments of available data and appropriate labeling.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps as Appropriate

The reviewer has no specific recommendations for postmarketing studies or risk management steps. Dose titration is appropriate if carried out according to the label. Serum testosterone levels should be measured by a reliable laboratory approximately 14 days after

. This will help assure that safe and desired serum levels of testosterone have been achieved. A potential dosing dilemma will be the need for an intermediary dose between 50 mg and 100 mg. those patients who absolutely require an intermediate dose of Testim™ will have no choice but to switch to an alternative approved product.

The sponsor and all healthcare providers involved with the treatment of androgen deficiency in men should be encouraged to report all significant AEs to the sponsor and/or the FDA.

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Testim™ contains 50 mg of testosterone 1% in 5 grams of gel per tube. It is a transdermal preparation applied to the shoulders and upper arms in doses of 50 mg (1 tube) or 100 mg (2 tubes). Testim™ was demonstrated to be safe and effective for the

Testim™ restored testosterone (T), dihydrotestosterone (DHT), and free testosterone levels to what is commonly accepted as the normal physiologic range (300-1000 ng/dL) in men.

Overall data

The primary efficacy evaluation is based on the single pivotal study AUX-202 described below.

The safety evaluation is based on the following eight studies:

- Four clinical pharmacology studies
  - two male to female transfer studies
  - one effect of washing study
  - one comparative PK study with an approved transdermal gel
- U.S. Phase 3 study AUX-202 (pivotal)
- European Phase 3 study AUX-204
- Two ongoing extension studies AUX-203 (U.S.) and AUX-208 (Europe)

Pivotal Study Design: Study AUX-202 was planned in a manner similar to the development of other FDA-approved testosterone products for hypogonadal males. The study was a randomized, active- and placebo-controlled, four arm, parallel-group, multicenter trial in adult males with morning serum testosterone levels ≤ 300 ng/dL. The four treatment arms were Testim™ 50 and 100 mg gel, matching placebo gel, and Androderm® transdermal patches (2 x 2.5 mg). Randomization was equal for each arm; the study was blinded for the three gel arms and open label for the active control Androderm® patch. Subjects were treated for a total of 90 days. Based on their Day 30 PK profile as interpreted per protocol by a blinded third party, subjects who were initially receiving Testim™ could have been titrated at Day 60 from either 50 to 100 mg, or from 100 to 50 mg, or may have been maintained on their initial dose. The placebo gel subjects were also randomly changed (increased or decreased) at Day 60 to keep the study adequately blinded in this arm.

Upon successful completion of the AUX-202 trial, all subjects were permitted to continue treatment with Testim™ in the 12-month, open label extension study AUX-203. This study is currently ongoing. The initial dose in the AUX-203 study is 50 mg/day; after 2 weeks of treatment, and at subsequent visits thereafter, the dose can be adjusted up to 100 mg or back down to 50 mg, depending on serum testosterone values and clinical symptoms. The ongoing results of the AUX-203 study were reported to the Division on May 6, 2002, and in the NDA safety update dated July 3, 2002.

2.2 Efficacy

The efficacy of Testim™ was evaluated in a single, active-comparator and placebo-controlled, parallel-arm, randomized, multicenter, 90-day, Phase 3 trial. The primary efficacy parameters were the average 24-hour serum total testosterone level (C_{avg}) and minimum serum total testosterone level (C_{min}). From these parameters two efficacy endpoints (Responder rates) were derived:

- Responder 1 rate: the percentage of subjects whose C_{min} and C_{avg} serum testosterone levels were between 300 and 1000 ng/dL, inclusive
- Responder 2 rate: the percentage of subjects whose C_{avg} testosterone level was between 300-1000 ng/dL, inclusive [this would include all Responder 1 subjects + those with a C_{min} < 300 ng/dL]

In the treatment of male hypogonadism, the Division believes that the attainment of "normal" serum testosterone levels in previously "hypogonadal" men is indicative of clinical efficacy. Currently, however, it is not clear how to best define "attainment of normal range serum T levels." The sponsor and Division agreed on a primary endpoint of Responder 1 rate (proportion of patients with average serum T and minimum serum T concentrations within the normal range of 300-1000 ng/dL). Responder rate 2 would also be analyzed. The Responder 1 rate endpoint tends to increase the "success rate" for products which produce serum levels of T above the minimum range but sometimes also above the maximum range.

Primary Efficacy – by Randomized Treatment Group

	Testim™ gel 50 and 100 mg	Transdermal patch	Placebo gel	95% CI
	% Responders based on C_{avg} and C_{min}			
	n=192	n=90	n=96	
Responder 1 rate	38.0	5.6	2.1	24.1 – 40.8
Nonresponders	62.0	94.4	97.9	

Overall, Testim™ gel at doses of 50 mg and 100 mg daily was effective in producing average serum total T concentrations within the normal range in the majority of hypogonadal men studied. There was evidence that clinical parameters consistent with hypogonadism, such as lean body mass, fat mass, and selected sexual functions, also improved, especially at the higher dose. There was evidence that titration of the Testim™ dose was effective in the manipulation of the optimal serum T level. However, there were some patients in whom serum T levels were too high, especially those patients receiving the 100 mg dose.

For the best possible assessment of efficacy (and safety), the biopharmaceutical and clinical reviewers evaluated several pharmacokinetic variables including C_{min}, C_{max}, C_{avg}, as well as several exploratory clinical endpoints including lean body mass and fat mass, sexual function parameters (libido, erectile function), and mood. Bone mineral density (BMD) data was not submitted at this time because the Division specifically requested BMD data after — months of testosterone treatment. BMD data will be submitted after the two open-label extension trials are completed and analyzed.

The risk of excessive serum T levels in the 50 mg daily dose group was very small. In order to minimize this risk, all patients will be advised to start on 50 mg daily, and all patients will be advised to have their serum T measured on approximately Day 14 after starting treatment. The risk of adverse events related to excess androgen should be greatly reduced by these simple instructions.

2.3 Safety

Safety data for Testim™ was based on the eight studies listed under overall data above. These studies provided sufficient data to make a conclusion about the safety of the product. Specific phototoxicity and cumulative irritation trials were not performed.

In a review of the literature, the most common adverse effects of a transdermal treatment gel are urogenital AEs including enlarged prostate, elevated PSA, and transient decreased urine flow. From the pivotal study AUX-202 in 407 subjects, analyses of laboratory parameters demonstrated small decreases in total cholesterol and HDL and small increases in PSA, RBC, hematocrit, and hemoglobin in the Testim™ subjects.

The sponsor's table below summarizes adverse events from study AUX-202 that were judged by the investigator to be related to treatment in ≥1% of Testim™-treated subjects and with greater incidence than in placebo-treated subjects.

Treatment-Emergent, Related AEs Reported in 1% or More Subjects*

Event	Testim™ gel		Placebo gel
	50 mg	100 mg	
Application Site Dryness	1%	0%	0%
Application Site Pruritus	0%	1%	0%
Benign Prostatic Hyperplasia	0%	1%	1%
Blood Pressure Diastolic Decreased	1%	0%	0%
Blood Pressure Systolic Increased	1%	0%	0%
Headache	1%	0%	0%
Hematocrit Increased	1%	0%	0%
Hemoglobin Increased	1%	0%	0%
Hot Flushes	1%	0%	0%

Event	Testim™ gel		Placebo gel
	50 mg	100 mg	
Insomnia	1%	0%	0%
Mood Swings	1%	0%	0%
Parosmia (distortion of smell)	1%	0%	0%
Polycythemia	0%	1%	0%
Soft Tissue Disorder	1%	0%	0%
Spontaneous Penile Erection	1%	0%	0%
Tearing Increased	1%	0%	0%
Unusual taste in mouth (dysgeusia)	1%	1%	0%

*AEs related to treatment ≥1% for either Testim™ treatment group and > placebo.

In the pivotal study, the incidence of serious adverse events (SAEs) in Testim™ treated subjects was low (6/206), consistent with the age and general health of the subjects studied. SAEs were relatively evenly distributed between the treatment groups, all six in the Testim™ arms being considered unrelated to treatment by the investigator.

Given the physiologic effects of testosterone on the prostate, a full review of laboratory PSA values, the International Prostate Symptom Score (I-PSS), results of digital rectal examinations (DREs), and of adverse events (AEs) involving the prostate was undertaken. The outcome of this review was the observation that testosterone delivered by the transdermal route does result in mild increases in "mean" PSA, comparable to increases cited in the literature. Similar numbers of patients were seen who increased or decreased from baseline across the Testim™, transdermal patch, and placebo groups. The magnitude of the increases in PSA, changes in I-PSS, or findings on DRE were not of a degree that caused concern in the Testim™ group. No meaningful differences were observed in the incidence of newly diagnosed benign prostatic hyperplasia between Testim™ and placebo, and only two cases of prostate cancer were diagnosed on therapy, both in patients treated with the transdermal patch. Testim™ was much better tolerated at the application site than the patch, and overall, presented a favorable safety profile.

The potential for dermal transfer of testosterone from a male to his female partner was evaluated in studies AUX-206 and AUX-209. At standardized time points after Testim™ 100 mg application by the male subjects to their shoulders and upper arms or abdomen, the couples engaged in a 15-minute session of vigorous rubbing so that the female partners gained exposure to the testosterone gel application site. In the abdominal application study AUX-206, the female partners showed definite transfer of testosterone at all time points. When males used a shirt to cover the abdomen at 15 minutes post application, the potential for transfer was markedly reduced. This prompted the sponsor to perform transfer study AUX-209 with the testosterone gel applied to the male's upper arm and shoulder in the prescribed normal manner. In general, a few female partners had minor increases in serum testosterone concentrations at some time during the 24-hour follow-up period. When males wore a long-sleeved T-shirt and rubbing started at 1 and 4 hours after application, the transfer of testosterone from male to female partners was prevented. Additional data from hand-washing studies indicated that thorough washing with soap and water removed all Testim™ from the skin surface. This data supports the use of thorough hand-washing after drug application and the washing of the male skin application sites prior to direct contact with others.

The overall risk/benefit ratio was sufficient for approval of Testim™ at the 50 mg and 100 mg dose.

2.4 Dosing, Regimen, and Administration

The recommended starting dose of Testim™ is 50 mg (one tube) applied once daily (preferably in the morning), immediately after opening the tube, to clean, dry intact skin only on the shoulders and/or upper arms. Applications sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed thoroughly with soap and water immediately after Testim™ has been applied. Studies of hand-washing show that Testim™ is effectively removed from the skin surface of the hand by thorough washing. Once the hands are washed and the application site is covered with clothing, there is little risk of transferring Testim™ to someone else due to bodily contact. If, however, direct skin contact is expected with someone else, the application site should be washed thoroughly with soap and water before that encounter. To assure adequate absorption of the testosterone, the application site should not be washed for at least two hours after gel administration.

Morning serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper testosterone levels are achieved. If the serum testosterone concentration is below the normal range (<300 ng/dL), the daily dose may be increased from 50 mg to 100 mg (two tubes). Testim™ should not be applied to the genitals or abdomen and is not approved for more than 100 mg as the daily dose.

2.5 Drug-Drug Interactions

There is no known effect of concomitant medications on the efficacy of Testim™. No special drug-drug interactions studies were performed by the sponsor.

2.6 Special Populations

The entire population in the USA and European Phase 3 trials were males with a serum testosterone level < 300 ng/dL at entry. The majority (>90%) were Caucasian with 60-65% being middle-aged, defined as being between 46-65 years of age.

Subjects with the following were excluded from the Phase III trials:

- Prostatic cancer, palpable prostatic mass(es), or serum PSA levels ≥ 4 ng/mL
- Clinically significant anemia or renal dysfunction
- Hepatic dysfunction
- Hyperparathyroidism or uncontrolled diabetes
- Generalized skin irritation or disease (e.g. psoriasis)
- Use of certain medications:
  - Any medications that could be considered anabolic (e.g. DHEA) or could interfere with androgen metabolism (e.g. spironolactone, finasteride, ketoconazole) were not permitted during the study
  - Estrogens, GnRH antagonists, human GH (within previous 12 months), sildenafil, apomorphine (within 30 days), or testosterone products (within 8 weeks for parenteral products, or 6 weeks for other preparations)

No special populations were studied.

Daniel Davis, MD, MPH
Medical reviewer, DRUDP
10-30-02

CLINICAL REVIEW

1.0 Introduction and Background

1.1 Description of drug

The formulation contains nine excipients in addition to the 1% testosterone. All excipients with the exception of oxacyclohexadecan-2-one have USP/NF monographs. Oxacyclohexadecan-2-one is a novel excipient being used for the first time in a topical drug product. The appropriate pre-clinical studies were performed on this excipient. The sponsor's topical gel is intended to provide consistent transdermal absorption of testosterone with a once daily application.

1.2 Regulatory history

On November 22, 2000, IND 61,307 was submitted to the Division for compound AA2500 (1% testosterone topical gel) for the AUX-TG-201 PK study. There were no safety issues with this original submission.

On January 17, 2001, the sponsor submitted Phase III protocol AUX-TG-202 for review. The Division recommended the following:

1. An active control design (rather than a placebo-controlled design)
2. Studying more than one dose with a pre-defined dose titration plan
3. A primary endpoint of the percentage of "responders."
4. Bone mineral density (BMD) assessments after ___ months.

On April 11, 2001, a teleconference was held with the sponsor to discuss the final Phase III protocol as amended. The 4-arm, active-controlled (Androderm® 2x 2.5 mg patches) and placebo-controlled trial using two doses (50 and 100 mg) of Testim™ was agreed to by the Division. Dose adjustment at Day 60 would be based on the full androgen profile drawn on Day 30 of the 12-week trial.

On May 17, 2001, the sponsor received a letter stating that the criteria for titration of the dose should be based only on the C_{avg} and not on C_{min}. This was acceptable to the sponsor. On June 29 and July 27 the sponsor submitted protocols for studies AUX-TG-206 (male to female transfer) and AUX-207 (effect of washing on T levels).

On August 1 and 8, 2001, the sponsor requested a Type B Pre-NDA meeting which was granted for October 4th. A teleconference (labeled as a guidance meeting) was held instead of a Pre-NDA meeting, because the sponsor did not have preliminary Phase III clinical data available for review by the Division. The following important points were made:

1. The transfer and washing PK study protocols -206 and -207 were acceptable.
2. The Division recommended that the Phase III -202 trial be designed as a non-inferiority trial in the STAT plan. The non-inferiority margin needed to be prespecified.
3. ___ will not appear in the final printed label (FPL).
4. The sponsor can submit stability data updates during the NDA review, but only up to three months prior to the goal date.

On December 31, 2001 the NDA was received; the CDR/CDER stamp date is 12/31/01 and the HFD-580 stamp date is 01-03-02.

1.3 Clinical background and important milestones in product development

The principal endogenous androgens, testosterone and dihydrotestosterone, are known to promote normal growth and development of the male sex organs and to maintain and promote development of the normal secondary male sex characteristics. These characteristics include the development of male pattern hair growth, laryngeal enlargement, vocal cord thickening, alterations in body musculature, fat distribution, and growth and maturation of the prostate, seminal vesicles, penis, and scrotum.

Androgens are also responsible for the growth spurt in adolescence and for the acceleration of linear bone growth. Androgens have been reported to increase protein anabolism and to decrease catabolism. There is also evidence that androgens stimulate the production of red blood cells by enhancing production of erythropoetin.

The term "male hypogonadism" refers to a condition in which the endogenous secretion of testosterone is "insufficient" or "inadequate" to maintain serum testosterone levels within the normal range. Some symptoms that may be associated with this condition include decreased sexual desire, changes in mood, regression of male secondary sex characteristics, and fatigue. It is also possible that prolonged hypogonadism may lead to osteoporosis.

Some conditions which may lead to a hypogonadal state in men include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's syndrome, exposure to chemotherapy or heavy metals ("primary hypogonadism") and pituitary-hypothalamic injury secondary to radiation, trauma, tumors or other idiopathic causes ("hypogonadotropic hypogonadism").

Currently, men with clinical hypogonadism may be offered testosterone replacement therapy in the form of intramuscular injections, transdermal patches and gels, or oral tablets. Each route of administration has its own specific risks and benefits.

The sponsor has developed a formulation of testosterone for the purpose of replacing endogenous testosterone in men with hypogonadal conditions. The method of treatment proposed is the daily application of a testosterone containing "gel" to the skin. Theoretically, upon application of the gel to clean, dry skin, the excipient materials in the formulation evaporate and the testosterone becomes incorporated into the epidermis. The sponsor believes that the epidermis actually serves as the "reservoir" for continuous systemic testosterone delivery during use of this gel.

1.4 Foreign marketing status

This product is not currently marketed in any other country.

1.5 Pharmacologically related agents

1. Testosterone intramuscular products, 200 mg by deep IM injection every 2-4 weeks: Virilon® IM and Delatestryl®
2. Methyltestosterone oral products: Android®, Virilon ®, and Testred®
3. Testoderm®- a 24-hour transdermal patch applied to the scrotum (4 or 6 mg/day); approved October 12, 1993

4. Androderm®- a 24-hour transdermal patch delivering ~5 mg testosterone per day; approved September 29, 1995
5. Testoderm® TTS system applied to the arm-back-upper buttock (60 cm^2 patch; 5 mg/day); approved December 18, 1997
6. AndroGel™- a transdermal gel applying 25 and 50 mg of 1% testosterone per application; approved February 28, 2000

2.0 Clinically relevant findings from chemistry, animal pharmacology and toxicology, and/or microbiology

2.1 Chemistry, Manufacturing and Controls

See the complete CMC review by the Division chemist.

2.2 Animal Pharmacology and Toxicology

Data on the new excipient, Oxacyclohexadecan-2-one, being used for the first time in a topical drug product was carefully reviewed and found to be safe. The other excipients and testosterone have been studied extensively prior to this drug application. Only limited animal toxicity studies were required of the sponsor. The Division reviewer found the Testim™ gel to be acceptable. See the complete review for details.

2.3 Microbiology

There was no microbiology data to review for this NDA.

3.0 Human Pharmacology (pharmacokinetics and pharmacodynamics)

3.1 Pharmacology Studies

Results from four Phase I clinical pharmacology studies were submitted with the NDA. These studies were reviewed for the PK/PD data and safety information. A total of 153 subjects participated in these studies. The table below summarizes the four studies.

Table 1: Phase I Clinical Pharmacology Studies

Study Name	AUX-201	AUX-206	AUX-209	AUX-207
No. of subjects	29	30 + 30 females	24 + 24 females	16
Type of study	**PK, Single dose,** 50 mg dose, crossover (to the comparator)	**Transfer of gel,** Single 100 mg **dose to abdomen**	**Transfer of gel,** Single 100 mg **dose to shoulder/ upper arm**	**Washing effect on** PK values after **single 100 mg dose application**
Comparative	**Yes-** active control (AndroGel™ 50 mg)	**Yes-** direct contact vs. t-shirt; contact at 1, 2, 8, 12 hours after application	**Yes-** direct contact vs. t-shirt; contact at 1, 4, 12 hours after application	**Yes-** compared baseline, 1, 2, 6 hour levels after dose application

3.2 Dose selection

Based on the results of study AUX-201, the sponsor elected to use a single aluminum tube containing 5 grams of product containing 50 mg of their 1% testosterone gel; the doses studied were 50 and 100 mg, delivered by applying either one or two tubes once daily to clean, dry intact skin of the shoulders and/or upper arms.

Reviewer's comment: Based on study data, the starting dose is safe in this patient population of hypogonadal males with a baseline testosterone (T) level < 300 ng/dL. A single 5 gram tube containing 50 mg testosterone, however, allows for an increase only to 100 mg (two tubes) and not an intermediary 75 mg of testosterone delivered to the skin.

4.0 Description of clinical data and sources

4.1 Overall data

The primary efficacy evaluation is based on the single pivotal study AUX-202 described in Section B. below. The safety evaluation is based on four clinical pharmacology studies (Table 1), one Phase 3 U.S. pivotal study AUX-202, one Phase 3 European study AUX-204, and the two ongoing extension studies AUX-203 (U.S.) and AUX-208 (Europe).

4.2 Design of pivotal USA clinical trial AUX-TG-202.01R (abbreviated as AUX-202 or -202)

Design: There are no specific FDA or ICH guidelines concerning the development of testosterone products as a replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Study AUX-202 was planned in a manner similar to the development of other FDA-approved testosterone products for men. The study was a randomized, active- and placebo-controlled, four arm, parallel-group, multicenter trial in adult males with morning serum testosterone levels ≤ 300 ng/dL. The four treatments arms were Testim™ 50 and 100 mg gel, matching placebo gel, and Androderm® transdermal patches (2 x 2.5 mg). Randomization was equal for each arm; it was blinded for the three gel arms and open label with the active control Androderm® patch. Subjects were treated for a total of 90 days. After 60 days, subjects who were initially receiving Testim™ could have been titrated from either 50 to 100 mg, or from 100 to 50 mg, or may have been maintained on their initial dose, based on their Day 30 PK profile as interpreted per protocol by a blinded third party. The placebo gel subjects were also randomly changed (increased or decreased) to keep the study adequately blinded in this arm.

Upon successful completion of the AUX-202 trial, all subjects were permitted to continue treatment with Testim™ in a 12-month, open label extension study AUX-TG-203.02 (abbreviated hereafter AUX-203 or -203). This extension study is currently ongoing. The initial dose in the AUX-203 study is 50 mg/day; after 2 weeks of treatment, and at subsequent visits thereafter, the dose can be adjusted up to 100 mg or back down to 50 mg, depending on serum testosterone values and clinical symptoms. The ongoing results of the AUX-203 study were reported in Submission No. 096 on May 6, 2002, and in the NDA safety update N-000 (BM) dated July 3, 2002.

Inclusion and Exclusion Criteria: the criteria were intentionally chosen to include a study population that represented the intended target population. All subjects were males, between 35 and 80 years of age, in generally good health.

They had the following key inclusion criteria:

- Screening morning serum testosterone ≤ 300 ng/dL
- One or more symptoms of testosterone deficiency (i.e., fatigue, reduced libido, or reduced sexual functioning of a non-vasculogenic or neurogenic nature)
- Body mass index between 18 and 31
- All screening lab tests within ± 20% of the normal range with the exception of LFTs, which were to be within the normal range

- Subjects with benign prostatic hypertrophy (BPH) and a normal PSA level, if felt by the investigator to not be at risk for urinary obstruction

The following exclusion criteria were used for the Phase III U.S. trial:

- Prostatic cancer, palpable prostatic mass(es), or serum PSA levels ≥ 4 ng/mL
- Clinically significant anemia or renal dysfunction
- Hepatic dysfunction
- Hyperparathyroidism or uncontrolled diabetes
- Generalized skin irritation or significant skin disease
- Positive test for Hepatitis B or C, or HIV
- Use of certain medications:
  - Any medications that could be considered anabolic (e.g. DHEA) or could interfere with androgen metabolism (e.g. spironolactone, finasteride, ketoconazole) were not permitted during the study
  - estrogens, GnRH antagonists, human GH (within previous 12 months), sildenafil, apomorphine (within 30 days), or testosterone products (within 8 weeks for parenteral products, or 6 weeks for other preparations)

Efficacy analysis:

The primary efficacy parameters in study AUX-202 were the average 24-hour serum total testosterone level (C_{avg}) and minimum serum total testosterone level (C_{min}). From these primary parameters two efficacy endpoints were derived:

- Responder 1 rate: the percentage of subjects whose C_{min} and C_{avg} serum testosterone levels were between 300 and 1000 ng/dL, inclusive
- Responder 2 rate: the percentage of subjects whose C_{avg} testosterone level was between 300-1000 ng/dL, inclusive [this would include all Responder 1 subjects + those with a C_{min} < 300 ng/dL]

The secondary efficacy parameters included assessments at Days 1, 30, 60, and 90 of the pharmacodynamic (PD) effects associated with testosterone use:

- Sexual function (sexual performance, motivation, desire, and enjoyment; erection parameters)
- Mood (positive/negative)
- Body composition determined by DEXA at Days -1 and 90 only (total body mass, lean body mass, fat mass, percent fat); DEXA scans were centrally analyzed by —
- Bone mineral density of the L1-L4 section of the lumbar spine (Days -1 and 90 only)

Additional secondary efficacy parameters were based on mean blood levels (C_{min}, C_{avg}, and C_{max}) of total and free testosterone, as well as on the major metabolite of testosterone, dihydrotestosterone (DHT) on Day 30 and Day 90. The ratio of C_{avg} DHT to C_{avg} total testosterone (DHT/T) was determined as a potential evaluation of testosterone effectiveness. Testosterone is a precursor that is converted by 5α-reductase to DHT or by aromatase to estradiol (E_2). DHT is the hormone responsible for many of the virilization effects of testosterone, while E_2 has no androgen effect. The change in the DHT/T ratio due to treatment may serve as an evaluation of effectiveness of the testosterone gel; the higher the ratio, the greater the potential for androgenic effects.

4.3 Postmarketing Experience

This specific product is not currently marketed in the USA or elsewhere in the world.

4.4 Literature Review

No special review of the medical literature was needed. The development plan for this product was carried out with input from the Division, and a similar topical testosterone gel for men was approved by the Division in February 2000. The risks and benefits of testosterone replacement therapy in hypogonadism males are well established and FDA-approved products have been in use for several years.

5.0 Clinical Review Methods

5.1 How Review was Conducted

Articles from books and peer-reviewed journals on the topic of testosterone replacement therapy in men were read for general background. Then the review was conducted by first reading the materials listed in section V. B. below. Special attention was paid to the proposed label and all SAEs from the four Phase 3 clinical studies. No special analyses were performed by this reviewer because there were no major issues in the approval of this topical testosterone gel.

5.2 Overview of materials consulted in review

The essential elements reviewed were the integrated summary of efficacy (ISE) and the integrated summary of safety (ISE) for Study AUX-202, the two safety update reports for the open label extension studies, the proposed label, and the case report forms (CRFs) for all the serious adverse events (SAEs). The clinical (medical officer's) review of a similar topical testosterone gel was also very helpful.

5.3 Overview of methods used to evaluate data quality and integrity

The data in the original NDA were compared to the data in the two major safety updates. No significant discrepancies were found. Any minor discrepancies were clarified with the sponsor. Some of the calculations (e.g. percentages, totals, confidence intervals) were checked for accuracy. No DSI inspections of clinical sites were held (see reviewer's comment). The CRFs for all SAEs in the AUX-202 study were reviewed.

> **Reviewer's comment: The decision to not have any site inspections was a result of the new draft policy from DSI which states that new NDAs do not automatically require clinical site inspections. Testim™ is not an NME, not first in its class, not intended for a novel population, not used for a new diagnostic category, and not delivered via a new route of administration. Site inspections were not indicated under these circumstances.**

5.4 Informed consent and standard of patient care

The subjects' informed consents and the Investigator Brochure were reviewed and felt to be adequate. Acceptable safety monitoring and stopping criteria were in place for the various Phase 1 and 3 studies.

5.5 Financial Disclosure Evaluation

This was performed by the Project Manager and found acceptable.

Integrated Review of Efficacy

6.1 Efficacy Conclusion

AA2500 (Testim™) gel is effective as replacement therapy for men with baseline serum testosterone levels ≤ 300 ng/dL. Since 57% of subjects who initially received the 50 mg dose did not require titration to the 100 mg dose, the recommended starting dose is 50 mg applied once daily (preferably in the morning). Based on the results of serum testosterone levels, some patients (especially older men with secondary hypogonadism) may require titration to Testim™ 100 mg. Titration to a lower dose is also a consideration at any time during replacement therapy.

6.2 Review of Clinical Trial AUX-TG-202.01R (herein abbreviated as AUX-202 or -202)

6.2.1 Design: There are no specific FDA or ICH guidelines concerning the development of testosterone as a replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Study AUX-202 was planned in a manner similar to the development of other FDA-approved testosterone products. The study was a randomized, active- and placebo-controlled, four arm, parallel-group, multicenter U.S. trial in adult males with baseline morning testosterone levels ≤ 300 ng/dL. The four treatment arms were Testim™ 50 and 100 mg, matching placebo gel, and Androderm® patches (2 x 2.5 mg). Randomization was equal for each arm; it was blinded for the three transdermal gel arms and open label for the active control Androderm® transdermal patch. Subjects were treated for a total of 90 days. After 60 days, subjects who were initially receiving Testim™ could have been titrated from either 50 to 100 mg, or from 100 to 50 mg, or may have been maintained on their initial dose, based on their Day 30 PK profile as determined by a blinded third party. The placebo gel subjects were also randomly changed to keep the study adequately blinded in this arm.

Upon successful completion of the trial, all subjects were permitted to continue treatment with Testim™ in a 12-month, open label extension study (study AUX-TG-203.02). This study is currently ongoing. The initial dose was 50 mg/day; after 2 weeks of treatment, and at every visit thereafter, the dose could be adjusted up to 100 mg or back down to 50 mg, depending on serum testosterone values. Some preliminary results of the AUX-203 study were reported in NDA submission N-000 (BM) on July 3, 2002.

6.2.2 Inclusion and Exclusion Criteria: the criteria were chosen to include a study population that represented the intended target population. Per protocol, all subjects were males, between 18 and 80 years of age, and in generally good health. They had the following key inclusion criteria:

- Screening morning serum testosterone ≤ 300 ng/dL
- One or more symptoms of testosterone deficiency (i.e., fatigue, reduced libido, or reduced sexual functioning of a non-vasculogenic or neurogenic etiology)
- Body mass index between 18 and 31

Subjects with the following were excluded from the Phase III trial:

- Prostatic cancer, palpable prostatic mass(es), or serum PSA levels ≥ 4 ng/mL
- Clinically significant anemia or renal dysfunction

- Hepatic dysfunction
- Hyperparathyroidism or uncontrolled diabetes
- Generalized skin irritation or disease (e.g. psoriasis)
- Use of certain medications:
  - Any medications that could be considered anabolic (e.g. DHEA) or could interfere with androgen metabolism (e.g. spironolactone, finasteride, ketoconazole) were not permitted during the study
  - Estrogens, GnRH antagonists, human GH (within previous 12 months), sildenafil, apomorphine (within 30 days), or testosterone products (within 8 weeks for parenteral products, or 6 weeks for other preparations)

6.2.3 Demographic and Baseline Population Characteristics:

The demographic and baseline population characteristics were comparable across the four treatment groups. All the enrolled subjects were male, and the majority (> 90%) were Caucasian. Between 60-65% of the study population was middle-aged, defined as being between 46 and 65 years of age; the median age was 58.0 years. Around 11% were age 18-45, and ~25% were > 65 years of age. Most subjects (~65%) were diagnosed with secondary hypogonadism of unknown etiology, but perhaps associated with aging. A range of 27-35% had secondary hypogonadism of identifiable etiology, while 2.1-7.6% were diagnosed as primary hypogonadism. There were no significant differences between treatment groups with respect to demographics or baseline characteristics of hypogonadism.

> **Reviewer's comment: By protocol, the trial was randomized and partially blinded [for AA2500 gel vs. placebo gel]. The four treatment groups appear to be well balanced at baseline with respect to the demographic and disease characteristics [age, race, and etiology of hypogonadism] that were analyzed. Data on socioeconomic parameters was not collected and therefore not analyzed.**

6.2.4 Study Disposition:

In total, 407 subjects were randomized in the clinical trial. Of these subjects, 353 (86.7%) completed the 12-week trial. In the Testim™ and placebo groups, 90 and 92%, respectively, completed the study, while 76% of the Androderm® treated group did so. General details of subject disposition are presented in Table 2. Discontinuations due to AEs are discussed in greater detail in the Safety Section of this review.

Table 2: Subject Disposition

	AA2500 gel 50 and 100 mg/d	Androderm® patch 5 mg/d	Placebo gel	Total
Randomized	N = 206	N = 102	N = 99	N = 407
Completed Day 90	89.8%	75.5%	91.9%	86.7%
Discontinued	10.2%	24.5%	8.1%	13.3%
Adverse Event	2.4%	16.7%	2.0%	5.9%
Protocol Violation	0.5%	2.0%	1.0%	1.0%
Withdrew Consent	2.9%	4.9%	3.0%	3.4%
Lost to Follow-Up	1.9%	0.0%	1.0%	1.2%
Other	2.4%	1.0%	1.0%	1.7%

Reviewer's comment: Only 6 Testim™ patients discontinued due to any AE. These 6 subjects are discussed in this review's section 7.6 on Premature discontinuations (page 36). The proposed labeling also reflects this result.

6.2.5 Primary Efficacy analysis:

The study was designed as a titration study. The subjects on AA2500 were evaluated on Day 30 with respect to serum testosterone values. On Day 60, predetermined increases or decreases in the dose were then made per protocol.

The primary efficacy parameters in study AUX-202 were the average 24-hour serum total testosterone level (C_{avg}) and minimum serum total testosterone level (C_{min}). From these parameters two primary efficacy endpoints were derived:

- Responder 1 rate: the percentage of subjects whose C_{min} and C_{avg} serum testosterone levels were between 300 and 1000 ng/dL, inclusive
- Responder 2 rate: the percentage of subjects whose C_{avg} testosterone level was between 300-1000 ng/dL, inclusive [this would include all Responder 1 subjects + those with a C_{min} < 300 ng/dL]

The secondary efficacy parameters included assessments at Days 1, 30, 60, and 90 of PD effects associated with testosterone:

- Sexual function (sexual performance, motivation, desire, enjoyment; erection parameters)
- Mood (positive/negative)
- Body composition determined by DEXA at Days 1 and 90 only (total body mass, lean body mass, fat mass, percent fat)
- Bone mineral density of the lumbar spine at Days 1 and 90 only

Additional secondary efficacy parameters were based on mean blood levels (C_{min}, C_{avg}, and C_{max}) of total and free testosterone, as well as on the major metabolite of testosterone, dihydrotestosterone (DHT) on Day 30 and Day 90. The ratio of C_{avg} DHT to C_{avg} total testosterone (DHT/T) was determined as a potential evaluation of testosterone effectiveness. Testosterone is a precursor that is converted by 5α-reductase to DHT or by aromatase to estradiol (E_2). DHT is the hormone responsible for many of the virilization effects of testosterone, while E_2 has no androgen effect. The change in the DHT/T ratio due to treatment may serve as an evaluation of effectiveness of the testosterone gel; the higher the ratio, the greater the potential for androgenic effects.

Three subgroups were analyzed by the sponsor as follows:

- Age (years): 18-45, 46-65, >65
- Race: Caucasian, Black, or Other
- Etiology of hypogonadism: primary, secondary (excluding aging), aging

Reviewer's comment:

6.2.6 Primary Efficacy Response Rates

Responder 1 rate, defined as the percentage of subjects in whom both C_{avg} and C_{min} serum testosterone was normalized between 300-1000 ng/dL (inclusive) was one of two primary efficacy endpoints. Approximately 44% of the subjects who used Testim™ 100 mg and 25% who used Testim™ 50 mg at the time of their last observation were responders compared to 6% for Androderm®. Responder 2 rate, defined as the percentage of subjects whose C_{avg} for total testosterone was > 300 ng/dL, was the other primary efficacy endpoint. The Responder 2 rate with Testim™ 100 mg was ~77%, with Testim™ 50 mg 68%, and with Androderm® was 59%.

Table 3 shows the sponsor's summary of response rates and the confidence interval (CI) for the modified intent-to-treat (MITT) population.

Table 3: Overall Response Rates in the MITT Population

Response type[1]	Treatment at Last Observation				Confidence Interval	
	50 mg AA2500 (N= 60)	100 mg AA2500 (N= 132)	Androderm (N= 90)	Placebo (N= 96)	50 mg vs. Patch	100 mg vs. Patch
Responder 1	25.0%	43.9%	5.6%	2.1%	7.5 to 31.4*#	28.7 to 48.1*#
Responder 2	68.3%	76.5%	58.9%	11.5%	-6.1 to 25.0	5.2 to 30.1*#
*satisfies non-inferiority hypothesis #satisfies superiority hypothesis						

[1]Responder 1 = C_{min} **and** C_{avg} between 300 ng/dL and 1000 ng/dL

Responder 2 = C_{avg} between 300 ng/dL and 1000 ng/dL [C_{min} < 300 ng/dL]

Reviewer's comment: It should be noted that Androderm® was dosed only up to 5 mg per day, as opposed to the labeled maximum daily dose of 7.5 mg per day. This was done by the sponsor despite the Division's recommendation to the contrary.

Total T, Free T, and DHT Levels

Treatment with AA2500 100 mg resulted in significant increases from baseline in the mean C_{avg}, C_{min} and C_{max} for total testosterone, free testosterone, and DHT compared to treatment with Androderm®. Treatment with AA2500 50 mg resulted in significant increases from baseline in the mean C_{avg} for free testosterone and DHT. The effect of AA2500 50 mg was also significant in terms of the increase in the mean C_{min}, compared to Androderm®, for all of the androgens measured. The increase in mean C_{max} induced by AA2500 50 mg was significant for DHT. The DHT/testosterone ratio increased significantly in subjects receiving AA2500 50 mg and 100 mg. Mean changes for C_{avg} and C_{min} are summarized in sponsor's Tables 4 and 5 for the overall results in the MITT population.

Table 4 Summary of Mean C_{ave} Changes (± SD) from Baseline to LOCF

Androgen	Statistic	Treatment at Last Observation			
		50 mg AA2500	100 mg AA2500	Androderm	Placebo
Total T	n	59	130	88	94
	Baseline	260.8	223.3	236.3	218.6
	Mean Change	148.4 ± 294.0	276.5 ± 237.2 ***	107.2 ± 150.3	-5.1 ± 60.3
	Range				
Free T	n	59	130	88	94
	Baseline	9.0	8.7	8.6	8.4
	Mean Change	6.0 ± 12.1 *	10.5 ± 9.5 ***	3.8 ± 5.0	-0.5 ± 2.1
	Range				
DHT	n	56	127	86	89
	Baseline	127.9	102.0	115.7	102.7
	Mean Change	301.2 ± 235.7 ***	413.8 ± 255.0 ***	48.3 ± 74.9	14.4 ± 66.7
	Range				
Significant versus Androderm® at: * $p \leq 0.05$; *** $p < 0.001$					

T = testosterone (ng/dL for total T, pg/mL for free T); DHT = dihydrotestosterone (pg/mL)

Table 5 Summary of Mean C_{min} Changes (± SD) from Baseline to LOCF

Androgen	Statistic	Treatment at Last Observation			
		AA2500 50 mg	AA2500 100 mg	Androderm	Placebo
Total T	n	59	130	88	94
	Baseline	208.4	177.9	192.9	171.6
	Mean Change	47.0 ± 159.6***	139.0 ± 181.9***	-30.6 ± 100.7	-3.4 ± 59.3
	Range				
Free T	n	59	130	88	94
	Baseline	7.3	6.9	6.9	6.5
	Mean Change	1.7 ± 6.4***	5.0 ± 6.6***	-1.1 ± 3.4	-0.2 ± 2.0
	Range				
DHT	n	56	127	86	89
	Baseline	92.5	70.6	82.9	72.2
	Mean Change	209.8 ± 199.9***	297.7 ± 213.4***	21.0 ± 50.7	16.1 ± 52.6
	Range				
Significant versus Androderm® patch at: *** $p < 0.001$					

T = testosterone (ng/dL for total T, pg/mL for free T); DHT = dihydrotestosterone (pg/mL)

Reviewer's comment: It is unclear why the baseline data for T, free T, and DHT is not identical for the 4 treatment groups in the two tables above. The n values are the same, as would be expected.

6.2.7 Secondary Efficacy Analysis:

Sexual Function

There were four main sexual function parameters. They were derived from answers to a series of questions recorded in the telephone Interactive Voice Response System (IVRS). For performance, motivation, and spontaneous erections, the mean value reported is the average number of events per 7-day week. A weekly frequency was created based upon activities that were calculated as an average weekly occurrence rate [AWOR].

Activities measured for performance were orgasm, ejaculation, intercourse, masturbation, and erection in response to a sexual activity. Items measured for motivation were sexual daydreams, anticipation of sex, sexual interaction with partner, flirting by subject, and flirting by other towards subject. The evaluation of spontaneous erections was based upon questions pertaining to the number of spontaneous nighttime and daytime erections. This was calculated as an average weekly occurrence rate.

Desire was based upon a single question pertaining to overall sexual desire, as scored on a 0 to 7 categorical scale (0 = none to 7 = very high). It was calculated as a mean daily score.

Testim™ 100 mg: Treatment with AA2500 100 mg resulted in definite improvement in sexual function, in terms of each of these parameters: motivation, desire, performance and the incidence of spontaneous erections, compared to placebo. Data collected at Days 30 and 60 reveal significant differences from placebo early in treatment with AA2500 100 mg. Based on subjects applying the 100 mg dose, with measurements at baseline and at Day 30, the response at Day 30 showed increases in sexual activity of 123%, and the number of days with spontaneous erections increased by 137%. In general, these results were maintained at Day 90 with increases of 62% in sexual activity and 78% in the number of days with spontaneous erections.

Testim™ 50 mg: Although the AA2500 50 mg group showed improvement from baseline in each of these parameters, no statistically significant differences compared to placebo were obtained.

Reviewer's comment: These improvements in sexual function are expected with testosterone replacement therapy. With the caveat that the sexual function parameters may not have been derived from validated instruments, it is still interesting to note statistically significant differences between the 100 mg treatment group and only non-statistically significant "improvement" in the 50 mg group, compared to placebo.

Sponsor Table 6 shows a summary of mean changes from baseline to LOCF in the four parameters measured for sexual function in the MITT population.

Table 6 Summary of Mean Changes (± SD) in Sexual Function from Baseline to LOCF

Sexual Function Parameter	Statistic	Treatment at Last Observation			
		50 mg AA2500 (N= 59)	100 mg AA2500 (N= 117)	Androderm (N= 84)	Placebo (N= 92)
Motivation	Baseline	1.5	1.8	1.6	1.5
	Mean Change	0.3 ± 1.4	0.6 ± 1.4†	0.5 ± 1.3	0.2 ± 1.2
Desire	Baseline	2.2	2.4	2.1	2.1
	Mean Change	0.6 ± 1.1	1.0 ± 1.3†	0.8 ± 1.2	0.5 ± 1.0
Performance	Baseline	0.8	0.8	0.7	0.8
	Mean Change	0.3 ± 1.0	0.5 ± 1.2†	0.4 ± 0.7	0.2 ± 0.9
Spontaneous Erection	Baseline	0.8	0.9	0.9	1.0
	Mean Change	0.3 ± 1.3	0.7 ± 1.5†	0.4 ± 1.2	0.1 ± 1.0

Significant versus Placebo at: † $p \leq 0.05$

Mood

Neither dose of AA2500 had a significant effect on mood, in terms of increasing positive mood or decreasing negative mood.

Body Composition

The body composition variables were measured by dual source X-ray absorptiometry (DEXA) scan. AA2500 100 mg increased lean body mass (LBM) to a greater extent than either of the control groups. The change with the AA2500 100 mg dose resulted in an average increase in LBM of 1.7 kg from the baseline of 61.1. Changes in total body mass were minimal and there was no evidence of statistically significant differences having occurred between the treatment groups.

Both doses of AA2500 resulted in a significantly greater decrease in both the fat mass (FM) and the percent of body fat (%F) than was reported in the placebo-treated groups. According to the sponsor, the actual mean FM decrease of 0.8 kg with the AA2500 treatment represented a clinically meaningful effect after 90 days of treatment.

Reviewer's comment: **The difficulty with mean changes is that it does not take into account the percentage of subjects in whom there was a meaningful increase or a decrease in the parameter being measured.**

Analysis of Dose Response or Blood-Level Response

Since blood levels of testosterone constitute the primary efficacy endpoints, and the dose was titrated to produce normalization of testosterone levels, formal dose-response analyses have not been performed by the sponsor. However, as may be expected, blood levels of testosterone and

the Responder 1 Rate based on those blood levels, were higher among subjects who received AA2500 100 mg compared to subjects who received AA2500 50 mg. Responder 1 Rate among subjects who used the AA2500 100 mg dose was slightly less than proportional to the dose, with about a 1.75 fold increase in response vs. a 2-fold increase in the dose. Responder 2 Rate was slightly higher among subjects who used the 100 mg dose compared to subjects who used the 50 mg AA2500 dose.

The changes from baseline in C_{avg} levels of total and free testosterone were approximately proportional to dose. However, C_{avg} DHT levels tended to be less than proportional to dose. In contrast, the changes from baseline in C_{min} levels of free and total testosterone were greater than proportional to dose (almost a 3-fold increase in levels with a doubling of the dose).

There was a clear dose-response effect of AA2500 with regard to sexual function in the four main parameters measured at Day 90.

No dose-response effect of AA2500 with regard to the change in fat mass or the ratio of fat mass to total body mass composition was noted. Both doses produced significant decreases in these parameters, suggesting a threshold effect at the 50 mg dose level.

> **Reviewer's comment: The reviewer agrees with the above sponsor conclusions. It should be noted, however, that the conclusions are based on a maximum of 90 days treatment. Analyses of the three subgroups [age, race, and etiology] did show some differences.**

6.2.8 Long-term effectiveness, tolerance, and drug withdrawal:

Upon completion of the AUX-202 trial, subjects were permitted to continue treatment with AA2500 in a 12-month, open label extension study (AUX-203). As of November 21, 2001, 227 subjects had been enrolled in this study; 17 have discontinued, and none have yet completed the trial. As this trial is still ongoing, further efficacy results of the extension study were not available for the sponsor's ISE. However, recent published literature indicates that the beneficial effects of testosterone replacement therapy are maintained following treatment with a 1% hydroalcoholic testosterone gel for up to 6 months. The results of Wang et al.[1] also indicate the beneficial effects of testosterone with regard to sexual function, mood, muscle strength, and body composition are maintained after 6 month of treatment using a 1% gel formulation, suggesting that tolerance does not occur. It is assumed that the beneficial effects of testosterone are not maintained upon discontinuation of treatment in men with hypogonadism, but the effect of withdrawal has not been assessed with AA2500.

> **Reviewer's comment: In the updated ISS submitted on July 3, 2002 (with a cutoff date of March 15, 2002), no further data on efficacy was provided. As of the March 15th date, 291 subjects were enrolled in the extension study AUX-203, 64 subjects have discontinued, and none have completed the study. Enrollment is complete and the last subject will finish the study in December 2002. Comments on safety (SAEs and AEs) are made in the safety section of this review.**

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[1] Wang C, Swerdloff RS, Iranmansesh A, et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. J. Clin Endocrinol Metab. 2000; Vol 85(8):2839-2853.

6.2.9 Drug-Demographic Interactions

The three subgroups analyzed were age, race and etiology of hypogonadism.

Age:
Men of different age groups may respond differently to transdermal administration of testosterone with regard to the normalization of testosterone and DHT levels as well as the pharmacodynamic effects of testosterone. To a certain extent this difference may be a reflection of the wide spectrum of signs and symptoms associated with the condition we call "hypogonadism". However, there can also be differences with respect to metabolism (both quantitative and qualitative) as well as permeability of the skin as a function of age that can affect response to exogenously administered testosterone. Therefore all primary and secondary efficacy parameters were analyzed by the sponsor by three age categories: 18-45, 46-65, and >65 years of age. The sample size of the youngest age group was small, accounting for only about 11% of the subjects who took AA2500 and about 6% of the subjects who used Androderm. This skewing of the data to the older age groups made statistical interpretation of the results difficult in some cases.

Responder rates by age: For those subjects who took AA2500 100mg, Responder 1 rate ranged from 33% to 45% in the three age groups, consistent with the overall results. For those subjects who took AA2500 50 mg, the Responder 1 rate ranged from 24% to 29% across the three age groups, slightly lower than the rates with AA2500 100 mg and higher than Androderm® rates [0 to 7.4%].

For those subjects who took AA2500 100 mg, Responder 2 rate ranged from 60% to 80% across the three age groups, while the Responder 2 rate for the AA2500 50 mg subjects ranged from 68% to 71%. These results were consistent with the overall results. Responder 2 rates for the comparator patch in all subjects older than 45 (N = 85), ranged from 57% to 70%.

> **Reviewer's comment: Responder 2 rate is obviously a more liberal evaluation of the testosterone level response than the Responder 1 rate, The data suggest that all age groups can benefit from treatment with AA2500 at both the 50 mg and 100 mg dose. The correct dose will depend on the subject's serum testosterone level after treatment is initiated with the 50 mg dose.**

Testosterone parameters by age:

C_{avg}: Subjects in all age groups who received either 50 or 100 mg AA2500 showed increases in the 24-hr average concentration (C_{avg}) for total testosterone, free T, and DHT compared to baseline. For subjects who received AA2500 100 mg, the increases resulted, in many cases, in more than a doubling of the baseline mean C_{avg} concentrations of testosterone or DHT. The increases were statistically significant relative to the Androderm® patch for each androgen measured within each age group, with the exception of total and free testosterone in the 18-45 age group (N = 14 for AA2500 100 mg; N = 5 for the patch).

For subjects who used AA2500 50 mg, the increases from baseline in C_{avg} for total and free testosterone among subjects in the middle-aged and oldest age groups were comparable to those observed for the patch. However, for all age groups the increase in C_{avg} DHT following treatment with AA2500 50 mg was significantly higher than that observed following treatment with the patch.

C_{min}: Subjects in all age groups who received either AA2500 50 or 100 mg showed increases in the C_{min} for each androgen level measured at Day 90 compared to baseline. For subjects who used AA2500 100 mg, the mean increases from baseline in C_{min} were statistically significant relative to the patch for every androgen measured within each age group. For subjects who used AA2500 50 mg, the mean increases from baseline in C_{min} were statistically significant relative to the patch for every androgen measured for all age groups, with the exception of total and free testosterone in the oldest age group.

C_{max}: Subjects in all age groups who received either AA2500 50 or 100 mg, showed increases in the C_{max} for each androgen compared to baseline. For subjects who used AA2500 100 mg, the increases resulted, in many cases, in more than a doubling of the baseline mean C_{max} concentrations of the androgens measured. The increases were statistically significant relative to the patch for each androgen level measured within each age group, with the exception of total and free testosterone in the youngest age group. Among subjects who used AA2500 50 mg, the mean change from baseline in C_{max} for DHT was consistently and significantly higher for all age groups compared to the patch. Additionally, for the youngest subjects, the increase in mean C_{max} for free testosterone relative to the patch, was significant.

Significant increases from baseline in the mean ratio of C_{avg} DHT to C_{avg} total testosterone were observed in both middle-aged and older subjects taking either dose of AA2500 compared to the change in subjects who used the patch. In general, the increases represented more than a doubling in the ratio from baseline.

> **Reviewer's comment: Overall, the AA2500 gel performed well, with the 100 mg dose clearly increasing the three PK parameters for the three measured androgens more effectively than the 50 mg dose and much more effectively than the transdermal patch. No dose titration was permitted for the patch subjects, Furthermore, the study was obviously not blinded to the active comparator [study gel vs. comparator patch].**

Mood, Libido and Sexual Activity by age: The sponsor assessed sexual function information using a questionnaire that they believed to be validated and that used the IVRS system to collect data. Sexual motivation, performance, and spontaneous erection were measured as an average total incidence over a 7-day period prior to the assessment period. Every parameter of sexual function was improved using LOCF relative to baseline in middle-aged subjects who used AA2500 100 mg. Interestingly, the effect of AA2500 100 mg was not statistically significant for any of the sexual function parameters in the youngest subjects. Furthermore, in the oldest subjects, neither dose of AA2500 appeared to induce any significant change from baseline in any parameter of sexual function.

Positive and negative moods were scored on a 7-point scale and average scores were assessed at each visit. Decreases from baseline represented improvements in negative mood scores. Neither dose of AA2500 appeared to induce any significant improvement at Day 90 from baseline relative to either patch or placebo in any age group.

> **Reviewer's comment: These results are difficult to interpret. The only clear result was the improvement in sexual function in middle-aged subjects [46 to 65 years old] who used the 100 mg dose. In the oldest subjects [~25% of the trial population; age > 65], neither dose of Testim™ had any "significant" effect on sexual function. Also**

of note is the finding that neither dose of Testim™ showed any improvement in mood at Day 90 compared to baseline.

Body Composition by age: Whole body DEXA was used to assess the following endpoints at Days 1 and 90: total body mass (TBM), lean body mass (LBM), fat mass (FM), percent fat (FM/TBM). Beneficial effects on body composition were seen in the youngest and oldest subjects treated with AA2500. Compared to placebo treatment, treatment with AA2500 100 mg resulted in a significant increase from baseline in lean body mass and significant decreases in the ratio of fat mass to total body mass in the youngest and oldest subjects, but not in middle-aged subjects. Treatment with AA2500 50 mg also resulted in a significant effect on all three parameters of body composition relative to baseline in the oldest subjects compared to placebo treatment. Treatment with AA2500 50 mg demonstrated improvements in LBM and FM, but the level of change did not reach statistical significance in the other age groups.

Reviewer's comment: [redacted] the data was obtained only at baseline and Day 90 (not at Day 180), and shows significance only when analyzed by subgroup.

Race: Theoretically, men of different racial groups may respond differently to transdermal administration of testosterone with regard to the normalization of testosterone levels as well as the pharmacodynamic effects of testosterone. This may be due to differences in metabolism (both quantitative and qualitative) as well as difference in permeability of the skin that can affect response to exogenously administered testosterone. However, in the pivotal Study -202, the sample size of black subjects and those classified as 'other' were small, each accounting for only about 4% of the total number of subjects in the MITT population. Therefore, the sponsor provided only descriptive statistics by racial category for efficacy parameters.

Reviewer's comment: No conclusions can be drawn from the studies concerning any racial differences. Caucasians accounted for 92% of the study subjects; 4% were Black and 4% Other. The results in Caucasian subjects very closely reflect the overall efficacy results.

Etiology of Hypogonadism:
The etiology of hypogonadism can be grouped into two main categories: 1) primary and 2) secondary. The sponsor believes that normal aging itself may be a cause of secondary hypogonadism. This remains a matter of controversy in the academic urology community. According to the sponsor, in this NDA, of those subjects with a diagnosis of secondary hypogonadism, the majority were related to "aging". Since approximately 65% of subjects enrolled in this study were older men with secondary hypogonadism of no clear etiology, "aging" was examined as a category separate from primary and other secondary causes. Primary hypogonadism involves failure at the testicular level, while secondary causes may involve pituitary or hypothalamic failure or a combination of both. In older men without obvious primary causes of hypogonadism, the predominant end-pathology appears to be a decline in Leydig cell number in the testes and in the activity of the enzymes in the metabolic pathway regulating testosterone production. There also may be a decreased ability to increase testosterone production in response to increased gonadotropin stimulation.

Reviewer's comments: In Study AUX-202, the proportion of subjects with a diagnosis of primary hypogonadism was only about 5% of the total number of subjects in the MITT.

Response Rates by Etiology:
Among subjects with secondary etiologies (including "aging"), the Responder 1 rate for those who used AA2500 100 mg was higher than for the comparator transdermal patch. The Responder 1 rate for subjects who used AA2500 50 mg was higher than the active comparator among the subjects with a diagnosis of secondary hypogonadism with no clear etiology besides "aging" (N=40 for AA2500; N= 59 for patch).

Serum Androgen levels by Etiology:
Regardless of etiology of hypogonadism, all subjects who received either AA2500 50 or 100 mg showed increases in the 24-hr average (C_{avg}), minimum (C_{min}), and maximum (C_{max}) concentrations of the androgens measured at LOCF compared to baseline. The sample size of the entire group (N= 19) with primary hypogonadism was too small to draw any meaningful comparative conclusions.

For subjects who used the AA2500 100 mg at LOCF, the increases generally resulted in more than a doubling of the baseline mean C_{avg} concentrations of androgens. Among subjects who used AA2500 100 mg, the increases were statistically significant compared to the patch for each androgen measured for those with secondary hypogonadism including those with secondary hypogonadism of no clear etiology besides "aging". Among subjects who used AA2500 50 mg, only the increases from baseline in C_{avg} DHT were statistically significant compared to the transdermal patch.

> **Reviewer's comment: It is clear that both doses of AA2500 increase the serum testosterone parameters compared to baseline, regardless of the etiology of hypogonadism.**

Sexual Function, Mood, and Body Composition by Etiology:
For subjects with secondary hypogonadism with no clear etiology besides "aging" who used AA2500 100 mg, every parameter of sexual function was improved relative to baseline. The mean change from baseline was statistically significant compared to subjects who used placebo. No inferential statistics were performed in the subgroup with primary hypogonadism with respect to sexual function or mood due to insufficient sample size. Neither dose of AA2500 demonstrated any significant improvement in mood from baseline for subjects with secondary hypogonadism of any etiology.

Beneficial effects on body composition were seen in subjects treated with both AA2500 100 mg and 50 mg. Compared to placebo treatment, treatment with AA2500 100 mg resulted in significant decreases in fat mass (FM) and the ratio of FM to total body mass (TBM) in subjects with secondary hypogonadism of any etiology. In subjects with hypogonadism thought to be

associated with normal aging, treatment with AA2500 100 mg also resulted in significant increases in LBM compared to both placebo and the comparator patch. Treatment with AA2500 50 mg resulted in significant decreases from baseline in FM and in the ratio of FM to TBM among subjects with secondary hypogonadism compared to both placebo and patch treatment, but had no significant effect on LBM. Furthermore, the 50 mg dose had no significant effects on the three parameters of body mass composition in older subjects with secondary hypogonadism.

Reviewer's comment: The reviewer's analysis of the sponsor's data concludes the following:

1. Sexual function in older subjects with secondary hypogonadism of no clear etiology was improved with the 100 mg dose compared to placebo.
2. Sexual function in other subjects with secondary hypogonadism was not significantly improved with either dose.
3. Mood was not significantly improved with Testim™ use in any subgroup.
4. Treatment with the 100 mg dose had generally positive effects on body composition; the 50 mg dose was beneficial only for decrease in FM.

6.3 Sponsor and Reviewer's Efficacy Conclusions:

In the AUX-202 study report, the principal summarization of efficacy was for the "combined study group" at Day 90, with the titration group summary included as a secondary analysis. The summarization of efficacy in the sponsor's ISE, however, is based on the final dose (LOCF analysis). The analysis of results in the overall population indicated that AA2500 is effective in normalizing testosterone levels within the commonly accepted physiological range. Both AA2500 50 mg and 100 mg are effective, and show a statistically significantly higher response rate compared to Androderm®. There is a dose-response effect with regard to the responder rate, with a Responder 2 rate of 68% among subject who used 50 mg and about 77% among subject who used 100 mg, compared to 59% for the transdermal patch.

For changes from baseline in pharmacokinetic parameters (C_{avg}, C_{min}, and C_{max}) for total testosterone, free testosterone, and the active metabolite DHT, treatment with AA2500 showed increases in a dose-dependent fashion.

The sponsor believes that the finding of increases from baseline in the $C_{avg}DHT/C_{avg}$ total testosterone ratio induced by both the 50 and 100 mg doses of AA2500 is indicative of the effectiveness of AA2500 in normalizing testosterone in hypogonadal men. This, they believe, is confirmed by the effects on sexual function and body mass composition. Testosterone is a precursor (prohormone) that is converted in the skin by 5α-reductase to DHT, a more active androgen.

Treatment with the AA2500 100 mg resulted in improvement in sexual function, in terms of motivation, desire, performance and the incidence of spontaneous erections, compared to placebo. Treatment with AA2500 also had a positive effect on body mass composition, compared to placebo. The AA2500 100 mg increased lean body mass (LBM) and decreased fat mass (FM) and the ratio of FM to total body mass (TBM). The effect of the AA2500 100 mg on LBM and the FM/TBM was better than the effect of Androderm®. AA2500 50 mg also was associated with larger decreases in FM and FM/TBM compared to placebo.

Neither dose of AA2500 had a significant effect on mood, in terms of increasing positive mood or decreasing negative mood.

The principal focus of the ISE is on subset analyses based on demographic and baseline characteristics of age, race, and etiology of hypogonadism. Because of small sample sizes in some of the subgroups, statistical interpretation was not possible in these groups. In the analysis of results by age, there were a small number of subjects (42/378 = 11%) in the youngest age group (18-45). Similarly, generalization to all racial groups is difficult given that the study population was 92% Caucasian.

The results of these subset analyses, however, do support the general conclusion that AA2500, especially at the 100 mg dose, is effective as replacement therapy for hypogonadal men.

Since 57% of subjects who initially received AA2500 50 mg did not require titration to 100 mg, the recommended starting dose is 50 mg applied once daily (preferably in the morning). Based on serum testosterone levels, patients may require titration to AA2500 100 mg.

Reviewer's comment: **The reviewer agrees with the sponsor's conclusions as stated above [modifications in the text were made by the reviewer] with the following caveats:**

1. **Many of the comparisons that are statistically significant are not clinically significant (meaningful) or are based on a small sample size that makes it difficult to draw a solid clinical conclusion.**
2. **The starting dose should be 50 mg AA2500 gel. All patients will be advised to have their serum T measured approximately 14 days after initiation of therapy.**
3. **Titration of the dose, either an increase or a decrease, is appropriate based on serum testosterone levels drawn after at least 14 days of a given daily dose.**
4. **The label may reflect the findings from this study, but conclusions drawn from lumping data together [i.e., changes in mean values] must be used very cautiously.**
5.
6. **It is not clear that all instruments and measures used to assess secondary endpoints have been fully validated for the populations in which they were used.**

7.0 Review of Safety

In the original ISS (December 2001) and the updated ISS (July 2002 submission), AEs were analyzed by the following general categories:

1. Overall summary of tolerability and AE profile by treatment group
2. Treatment-emergent AEs (TEAEs) reported in 2% or more subjects, regardless of causality
3. AEs (≥ 1%) possibly or probably related to AA2500 treatment
4. Skin irritation assessment
5. Laboratory evaluations
6. Prostate assessments
7. SAEs and deaths
8. Discontinuations due to AEs

Reviewer's comments: The format or categories in the two ISSs are the same. The primary difference is with the study data covered. The original ISS covers only the All Treated Subjects population (ATS) from the US study AUX-202. This study was designed as a titration study. The subjects on AA2500 were evaluated at Day 30 with respect to serum testosterone values. On Day 60, those subjects on 50 mg could be increased to 100 mg and those on 100 mg could be decreased to 50 mg based on 1) serum testosterone level in response to treatment gel and 2) clinical symptoms. In the AUX-202 study report, safety summaries at Days 30 and 60 were presented by original randomization group. In addition, summaries at Day 90 or summaries based on the entire study period were presented by the combined AA2500 group. Adverse events were also summarized by the dose the subject was receiving at the start of the adverse event.

The updated (July 2002) ISS covers four clinical trials: the two Phase 3 trials (US and Europe) and their open label extension studies with a cutoff date of March 15, 2002. However, all SAE data up to June 30, 2002, regardless of study, was included in the updated ISS.

This reviewer's analysis of safety will concentrate primarily on the original ISS. When data or tables from the updated ISS are used, it will be specifically noted. Likewise, when the reviewer believes there is a notable difference between the two ISSs, a specific comment will be made.

7.1 Safety Conclusion (brief)

The benefit/risk ratio demonstrates a steady effect on normalization of testosterone with attendant improvement in physiology and sexual function with a low risk of adverse effects. The overall benefit/risk ratio favors making AA2500 available for commercial use.

7.2 Subject Exposure to Drug

Exposure was expressed in terms of the total number of subject-days for each dose/treatment. Since subjects receiving either 50 mg or 100 mg AA2500 may have been titrated, these subjects were counted under each dose of AA2500 they received. The total patient-days of exposure to AA2500 were 17,450 days in Study -202.

Exposure data for the extension Study -203 (cutoff date of 21 November 2001) were hand tabulated and combined with data from Study -202 in Table 7 below.

Table 7 Summary of Treatment Exposure- USA Studies -202 and -203

	AA2500 50 mg	AA2500 100 mg
	N=269	N=226
Days	**Number of Patients**	
1-30	137	47
31-60	38	49
61-90	52	62
91-120	35	45
121-150	5	14
151-180	2	9

Combined: AUX-202 and AUX-203 exposures. Includes patients from AUX-202 who did not enroll into AUX-203.

Reviewer's comment: The extent of exposure in the combined US trials was adequate to assess safety. The mean number of days of exposure to the 50 mg dose was approximately ~46 days. The mean number of days exposure to the 100 mg dose was approximately ~69 days [reviewer's calculations].

From the last updated ISS, further exposure data is provided in Table 8 from the four Phase 3 studies using a March 15, 2002 cutoff date.

Table 8 All Treated Subjects*: AA2500 Total Exposure from 4 Studies

Number days	≤ 90	91-180	181-270	> 270
Number subjects	137	204	140	32

*Exposure to AA2500 regardless of dose; data combined from studies -202 and -203 (USA), and -204 and -208 (Europe).

Reviewer's comment: This exposure is adequate for safety assessment of this testosterone product. From the two double-blind (placebo-controlled) studies -202 and -204, subjects using the 50 mg dose had 13,177 days of exposure, while subjects using the 100 mg dose had 16,426 days of exposure. In addition, at least 140 patients have received study drug for at least 180 days.

Study demographics

Baseline demographic characteristics for subjects in the pivotal USA Study -202 are presented on page 15 of the efficacy section of this review. When the subjects from the Phase 3 European study -204 are added, the baseline demographics were still comparable between treatment groups. The average age of the combined populations was 58 years. The mean subject height, weight, and BMI across all treatment groups was 70 inches (178 cm), 205 pounds (93 kg), and 29, respectively. The mean baseline testosterone level was 232 ng/dL. The treatment groups were balanced with respect to Caucasian race, the range from 92-96%.

Adequacy of safety assessment
As noted above in the comments about exposure to AA2500, there is adequate exposure to assess safety. The parameters studied by the sponsor are also appropriate and analyzed in this review.

7.3 Deaths
There were no deaths from the Phase 1 studies. From the four clinical trials, there was one death reported in a subject using AA2500 in the US open label extension study -203. This case is discussed here:

Patient # 1030/3259:

The patient was a 61-year-old Caucasian male, height 74 inches, weighing 278 pounds. Upon entry into the -202 study the patient had an abnormal ECG [poor R wave progression; nonspecific anterolateral T abnormalities] and was receiving Cardizem, Clonidine, and Cozaar for hypertension; Baycol for hyperlipidemia, and Glyburide for adult onset diabetes. The patient received AA2500 100 mg throughout the -202 study. He entered the -203 extension study on October 10, 2001 and was started on AA2500 50 mg; on October 23rd he was titrated to AA2500 100 mg/day.

On arrival of the paramedics at his house or [redacted] the subject was in cardiorespiratory collapse with agonal respirations and no apparent BP. This condition deteriorated to one of apnea and pulselessness. The patient was brought to the ER of an [redacted] nospital by paramedic ambulance with full cardiopulmonary resuscitation in progress. Intravenous atropine and epinephrine were administered in the ambulance and ER. The initial recorded ECG rhythm was asystole, which remained unchanged in the ER. With the moribund status and failure to respond to resuscitation, the resuscitation was suspended and the patient was pronounced dead. The investigator felt the event was not related to study drug.

> Reviewer's comment: **With the pre-existing hypertension, hyperlipidemia, and adult onset diabetes, it is difficult to determine the role of AA2500 100 mg as a contributing factor. The patient had been on this dose for more than 20 weeks at the time of the fatal event. He was 61, overweight, and had at least three different medical conditions that could contribute to a fatal cardiorespiratory collapse. It is this reviewer's opinion that AA2500 was probably not a significant contributing factor.**

7.4 Serious Adverse Events (SAEs)
A total of 43 subjects experienced as least one SAE during all (4) clinical studies of AA2500. Thirty-five SAEs occurred in subjects using AA2500, six in subjects using a testosterone patch, and one in a subject using placebo gel. SAE data as of June 30, 2002 are presented in the latest safety update. **A summary of the 35 subjects with SAEs on AA2500 is seen in Table 9.**

Table 9: Listing of Serious Adverse Events (SAEs)			
↓Subject #	Preferred Term	Causality	Reason for SAE
Blinded Studies AUX-TG-202 (USA) / Study AUX-TG-204 (Europe)			
AA2500 50 mg			
58041829	Pyelonephritis NOS	Not Related	Hospitalization
AA2500 100 mg			
10041109	Vertigo	Not Related	Hospitalization
10135629	Localized Infection †	Not Related	Hospitalization
10303213	Rectal Hemorrhage	Not Related	Hospitalization
10383902	Ischemic Coronary Artery Disease	Not Related	Hospitalization
10574801	Suicidal Ideation Depression Aggravated	Not Related Not Related	Hospitalization Hospitalization
10574810	Constipation Urinary Tract Infection NOS Pneumonia NOS	Not Related Not Related Not Related	Hospitalization Hospitalization Hospitalization
50183514	Asthma NOS †	Not Related	Hospitalization
50203702	Hip Fracture Joint Dislocation NEC	Not Related Not Related	Hospitalization Hospitalization
58041823	Chest Wall Pain Thyroid Function NOS Abnormal	Not Related Not Related	Hospitalization Hospitalization
58051913	Influenza	Not Related	Hospitalization
Study AUX-TG-208 (European open label extension)			
AA2500 50 mg or 100 mg			
57021210	Angina Pectoris	Possible	Hospitalization
57041031	Meniscus Removal	Not Related	Hospitalization
57044185	Transient Ischaemic Attack	Not Related	Medically Important
United Kingdom – Named Patient Basis			
AA2500 50 mg or 100 mg			
50032904	Colonic Polyp Colon Operation	Not Related Not Related	Hospitalization Hospitalization

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Table 9: Listing of Serious Adverse Events (continued)			
Subject #	**Preferred Term**	**Causality**	**Reason for SAE**
Study AUX-TG-203 (USA open label extension)			
	AA2500 50 mg or 100 mg		
10131613	Aortic Aneurysm † Carotid Artery Stenosis †	Not Related Possible	Hospitalization Hospitalization
10135605	Cardiac Failure Congestive Acute Respiratory Distress Syndrome	Possible Not Related	Hospitalization Hospitalization
10141712	Accidental Overdose	Not Related	Hospitalization
10232475	Bladder Cancer NOS	Not Related	Life Threatening
10242601	Headache NOS Abdominal Pain NOS	Not Related Not Related	Hospitalization Hospitalization
10303259	Cardio-respiratory Arrest	Not Related	Death
10323524	Peripheral Swelling Dyspnea NOS	Not Related Not Related	Hospitalization Hospitalization
10434311	Joint Dislocation NEC Arthralgia	Not Related Not Related	Hospitalization Hospitalization
10434318	Prostate Cancer NOS †	Not Related	Life Threatening
10474707	Meniscus Lesion	Not Related	Hospitalization
10512506	Pain NOS Back Pain Heart Rate Abnormal Abdominal Aneurysm	Not Related Not Related Possible Not Related	Hospitalization Hospitalization Hospitalization Hospitalization
10512517	Blood Glucose Increased	Possible	Hospitalization
10544542	Melaena Abdominal Pain Upper Nausea Loin Pain	Not Related Not Related Not Related Not Related	Hospitalization Hospitalization Hospitalization Hospitalization
10583068	Arthralgia Knee Operation	Not Related Not Related	Hospitalization Hospitalization
10654101	Deep Vein Thrombosis NOS † Pulmonary Embolism †	Possible Possible	Hospitalization Hospitalization
10654127	Cardiac Failure Congestive †	Not Related	Hospitalization
10682208	Spinal Fusion NOS †	Not Related	Hospitalization
10682218	Cholecystectomy	Not Related	Hospitalization
10695042	Asthma Aggravated	Not Related	Hospitalization
10745512	Diabetic Foot Ulcer	Not Related	Medically Important

SAE-serious adverse event; NOS-not otherwise specified
CAD-coronary artery disease; NEC-not elsewhere classified
UTI-urinary tract infection; PSA-prostate specific antigen
† Event ongoing

Reviewer's comment: This table lists all 35 subjects using AA2500 with reported SAEs from the 4 clinical trials up to the cutoff date of June 30, 2002. All the narrative summaries were reviewed; 13/35 (37%) of these subjects withdrew from the study, while the remaining 63% continued with the AA2500 study medication despite the SAE.

7.5 Treatment emergent adverse events (TEAE)

Treatment-emergent adverse events experienced by ≥ 2% of all treated subjects within at least one treatment group in Study AUX-202 is presented in Table 10 below.

Table 10: Treatment-Emergent AEs Reported in 2% or More Subjects, Regardless of Causality, by Treatment Received at Start of AE

Body/Organ System Preferred term	AA2500		Androderm	Placebo
	50 mg	100 mg	5 mg	
Subjects	103	149	102	99
	The numbers below are a % of the subjects enrolled			
Gastrointestinal Disorders				
Nausea	0	0	2.0	0
General Disorders/Administration Site Disorders				
Erythema	1.0	2.0	29.4	2.0
Rash	0	0.7	7.8	0
Pruritus	0	1.3	5.9	0
ASR NOS	0	0.7	5.9	1.0
Irritation	0	1.3	3.9	0
Pain NOS	0	0.7	1.0	2.0
Burning	0	0	2.0	0
Immune System Disorders				
Seasonal allergies	0	0	0	2.0
Infections and Infestations				
Nasopharyngitis	2.9	0.7	2.9	1.0
Investigations				
Blood Pressure Increased	1.0	1.3	1.0	2.0
Triglycerides Increased	0	0	0	2.0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1.9	2.0	2.0	5.1
Back pain	0	2.7	1.0	1.0
Muscle cramps	0	0	0	3.0
Neoplasms Benign, Malignant, and Unspecified				
BPH	0	2.0	0	1.0
Prostate CA NOS	0	0	2.0	0
Nervous System Disorders				
Headache NOS	1.9	0	2.0	0
Reproductive System and Breast Disorders				
Epididymitis NOS	0	0	2.0	0
Skin and Subcutaneous Tissue Disorders				
Acne NOS	0	0	0	2.0

ASR-application site reaction; NOS-not otherwise specified; BPH-benign prostatic hyperplasia; CA-cancer.

Reviewer's comment: The only AEs of note are the high incidence of skin related events due to the transdermal patch.

A summary of the adverse events judged to be at least possibly related to study drug that occurred in ≥1% of subjects in the AA2500 group and placebo groups in study -202 is presented in Table 11. As the data demonstrate, the incidence of drug-related adverse events for AA2500 subjects was low.

Table 11: Adverse Events Possibly (≥ 1%) or Probably Related to AA2500

	AA2500 gel		Placebo
MedDRA Preferred Term	50 mg (N=103)	100 mg (N=149)	
	Percent (%) of Subjects Reporting Event		
Polycythemia	**0**	**1**	**0**
Lacrimation Increased	**1**	**0**	**0**
Unpleasant taste in mouth	**1**	**1**	**0**
Application Site Erythema	**1**	**2**	**2**
Application Site Pruritus	**0**	**1**	**0**
Application Site Dryness	**1**	**0**	**0**
Spontaneous Penile Erection	**1**	**0**	**0**
Diastolic Blood Pressure Decreased	**1**	**0**	**0**
Systolic Blood Pressure Increased	**1**	**0**	**0**
Hematocrit Increased*	**1**	**0**	**0**
Hemoglobin Increased*	**1**	**0**	**0**
Soft Tissue Disorder NOS	**1**	**0**	**0**
Headache NOS	**1**	**0**	**0**
Insomnia	**1**	**0**	**0**
Parosmia (smell perversion)	**1**	**0**	**0**
Mood Swings	**1**	**0**	**0**
Hot Flushes NOS	**1**	**0**	**0**
BPH	**0**	**1**	**1**

Reviewer's comment: There are no values here that are of major concern. The table intentionally omits the data for the transdermal patch, as it is an approved product. *The overall AEs for all subjects treated with Testim™ showed 2 men (2/205 = 1%) with "polycythemia". No Testim™ subject had a Hgb >20 g/dL or a hematocrit ≥ 60%, so the 1 subject listed here was judged to be at least possibly "treatment related".

7.6 Premature discontinuations

From the July 2002 updated ISS, Table EE is presented listing a summary of the number of subjects who prematurely discontinued from the two blinded Phase 3 studies. A total of 614 subjects were randomized and received at least one treatment. The percentage of subjects prematurely discontinuing in the following groups was: AA2500 50 mg (8%), AA2500 100 mg (8%), placebo (8%), and testosterone patch (23%). There was a higher incidence rate of study discontinuation due to AEs in the testosterone patch groups (15%). The majority of these treatment-related discontinuations were due to application site reactions (skin irritation).

Table 12: Summary of Subject Disposition- Studies -202 (US) and -204 (Euro)

	AA2500* 50 mg/d	AA2500* 100 mg/d	Testosterone patch 5 mg/d	Placebo	TOTAL
Enrolled ⇒	N = 128	N = 217	N = 170	N = 99	N = 614
Completed Day 90	92%	92%	77%	92%	88%
Discontinued	8% (N= 10)	8% (N= 17)	23% (N= 39)	8% (N= 8)	12% (N= 74)
Adverse Event	3%	2%	15% (N=27)	2%	6%
Protocol violation	0%	1%	2%	1%	1%
Withdrew consent	2%	3%	4%	3%	3%
Lost to follow-up	2%	1%	0%	1%	1%
Other	1%	1%	1%	1%	1%

* AA2500 subjects summarized by last treatment received

Reviewer's comment: The completion rates above for AA2500 were >90% and better than the active comparator patch. The primary reason for the difference in completion rates is the discontinuations due to an AE. Of the 27 subjects using the testosterone patch and discontinuing because of an AE, 89% (24) discontinued due to a local skin reaction to the patch. By comparison, only one AA2500 subject [# 58041866 using the 100-mg dose] prematurely discontinued from a pivotal trial because of an unacceptable skin AE.

Premature discontinuations from Study -202 due to an AE while on AA2500

From the original ISS, there were six subjects using AA2500 in the US trial AUX-202 who discontinued from the 90-day study due to an AE. Herein, these patients are described in detail.

AA2500 50 mg/day:

Patient 10501827: A 66-year-old Caucasian male began AA2500 50 mg study treatment on 08 Aug 2001. On Study Day [redacted], the subject experienced severe mood swings and was treated with dehydroepiandrosterone BID. Concomitant medications at the time of the event included tamsulosin for benign prostatic hypertrophy; glyburide and metformin for non-insulin dependent diabetes mellitus; naproxen and chlorzoxazone for back pain; metoprolol for hypertension; and saw palmetto for prostrate health. The subject withdrew from the study on [redacted] because of the mood swings. The event abated after study drug withdrawal. According to the investigator, the event was probably related to study treatment.

Reviewer's comment: In this reviewer's opinion it is not probable that the AE was related to the study drug, because the lower 50 mg dose was used for only two days when the severe mood swings were experienced. Furthermore, the treatment with DHT is an obvious confounding factor.

AA2500 100 mg/day:

Patient 10041101: A 50-year-old Caucasian male began AA2500 100 mg study drug on 24 May 2001. The subject had a history of hypertension since 1995 that was being treated with benazepril. The subject's screening blood pressure was 128/84 mmHg and on Day 1 the blood pressure was 126/90 mmHg. On [redacted] the subject developed elevated blood pressure (results were not provided). The subject was treated with doxazosin 4 mg for the condition. The subject terminated from the study four days later because of the event. At the time of the termination visit, the subject's blood pressure was at 180/120 mmHg. According to the investigator, the event was possibly related to the study drug.

Reviewer's comment: This AE and discontinuation was probably not related to the study drug. The subject was on AA2500 for only 4 weeks and had a known history of hypertension. No details are given concerning possible changes in diet, medication compliance (for benazepril), etc.

Patient 10041109: A 73-year-old obese (222 lb.), Caucasian male began study drug with AA2500 100 mg on 25 Jun 2001. The subject had a history of non-insulin dependent diabetes mellitus since 1978, diabetic neuropathy of the extremities and spinal stenosis since 1996, hypertension, and osteoarthritis. Concomitant medications included glyburide and metformin; amitriptyline (study exception); furosemide; felodipine and benazepril; celecoxib and oxycodone. On —) the subject developed moderate vertigo and was admitted to the emergency room to rule out a possible cerebrovascular accident. The subject's most recent blood pressure prior to the event was 138/80 mmHg. An MRI of the head showed a small piece of calcium lodged in the fluid channel. The calcium was dislodged by physical positional manipulation. The study drug was discontinued the same day. According to the investigator, the event was not considered related to the study drug.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient 1038/3902: A 69-year-old Hispanic male began study treatment AA2500 100 mg on 23 Jun 2001. The subject had a history of hypertension since 1998 and was being treated with benazepril. On — , the subject was seen by his primary physician for a routine exam. The exam led to a referral to a cardiologist, who diagnosed the subject with coronary artery disease. The subject was hospitalized the same day and underwent an angiography that revealed a 50 to 60% blockage of the left middle coronary artery with pressure dampening; the left anterior descending coronary artery revealed 80 to 90% blockage mid vessel and 70% blockage distal vessel; the circumflex artery had 80 to 90% blockage distally; the right coronary artery was non dominant and patent. The estimated cardiac function was at 30 to 35% of normal capacity. The subject withdrew from the study the following day due to the condition. While in the hospital, the subject successfully underwent triple bypass surgery. According to the investigator, the event was considered severe in intensity and not related to the study drug.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient 10574801:
A 54-year-old Caucasian male (71 inches; 260 lb.) began study drug AA2500 100 mg on 26 Apr 2001. The subject had a history of hypertension, asthma, GERD, insomnia, depression, and anxiety and was receiving carbidopa-levodopa; venlafaxine and trazodone; and lorazepam. The subject was admitted to a medical center on — due to a concern about severe suicidal ideation and depression. After his family had found the subject with a gun, police were called, and the subject was subsequently confined to the medical center. The subject underwent a full psychiatric evaluation and medical work-up. The investigator was notified of the event on — and the study drug was withheld on — . The subject was discontinued from the study on — on the recommendation of Auxilium. Subject treatment for this occurrence included multiple, centrally acting medications, which would confound study assessments. According to the investigator, the event was not considered to be related to the

study drug. This subject was listed as discontinuing study drug for this adverse event on the adverse event CRF page. However, this subject was listed as not completing the study due to reason "Other – sponsor request" on the study completion page.

Reviewer's comment: Testosterone therapy can be associated with behavioral changes, mood changes, and depression. This subject already had such a history and was being treated with the above listed medications. The reviewer believes that the relationship to study drug is unlikely, but possible, given the medical history of this subject.

Patient 10574810: A 43-year-old Caucasian male began study treatment AA2500 100 mg on 30 May 2001. Concomitant medications included tizanidine and oxycodone for back pain; alprazolam for anxiety; zolpidem for insomnia; rofecoxib for osteoarthritis; lansoprazole for acid reflux; venlafaxine for depression; senna for constipation; and multivitamins for general health maintenance. The subject also had a recent history of constipation with impaction. On the Day — the subject was experiencing chills and malaise accompanied by a 102.8° Fahrenheit temperature and severe diarrhea. A urinalysis was performed that suggested a urinary tract infection. Ciprofloxacin 500 mg and levofloxacin 500 mg were started. The subject was admitted to the hospital the same day due to general decline in health. A chest CT showed pneumonia. Laboratory testing revealed a white blood count of 15.6 k/uL (NR = 4.00 – 11.00 k/uL). A diagnosis of chronic diarrhea secondary to lactose intolerance, pneumonia and a urinary tract infection was made. The study treatment was discontinued the same day due to these conditions. The subject's diarrhea improved with a lactose free diet. Follow-up chest x-rays showed questionable congestive heart failure on —, the subject's white count improved to 8.9 k/uL and a subsequent chest x-ray showed improvement in the congestive heart failure. The subject was discharged the same day in stable condition. Study drug was not restarted. According to the investigator, the events were considered severe in intensity and not related to the study drug.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

7.7 Clinical Chemistry

The incidence of clinically significant chemistry laboratory values was evaluated for all treated subjects participating in Study -202. Subset analyses by subject, age, and race were also performed on chemistry laboratory abnormalities. The results of this analysis demonstrate that only two parameters, fasting serum glucose and blood urea nitrogen (BUN), had an incidence of ≥1% of subjects with clinically significant values.

Carbohydrate metabolism

The overall incidence of clinically remarkable glucose levels (≥300 mg/dL) was 1%, 1.4%, 2.0%, and 1.0% for the AA2500 50 mg, AA2500 100 mg, Androderm®, and placebo groups, respectively.

It has been reported that supplementation of testosterone in hypogonadal men reduced levels of leptin and insulin. In Study -202, all subjects with serum glucose levels ≥ 300 mg/dL were documented to be pre-existing diabetics. No clinically significant changes from baseline were observed for serum glucose levels over the 90-day treatment period in any of the treatment groups (AA2500, Androderm® patch, and placebo) and there were no differences seen between groups.

BUN

A total of 3% of subjects had decreased BUN levels (≤8 mg/dL), while 3.8% of all subjects had increased BUN levels (≥30 mg/dL). Because there were a comparable number of decreased and increased BUN levels, these findings likely do not have any clinical significance. The incidence of abnormal (both high and low) BUN values was comparable across age groups (7%, 6.6%, and 6.8%, respectively, for the 18-45, 46-65 and >65 year age groups). The same results were found in the updated ISS.

Lipid metabolism

At Day 30, AA2500 100 mg reduced mean total serum cholesterol when compared to Androderm® patch and placebo. At Day 60, AA2500 100 mg maintained the reduction in total serum cholesterol as compared to Androderm® and placebo. The mean changes are detailed in sponsor's Table 13.

Table 13: Serum Cholesterol – Study AUX-202

	AA2500 50 mg	AA2500 100 mg	Androderm®	Placebo
	Cholesterol (mg/dL)			
Baseline	204.8	205.7	196.5	199.4
Day 30	199.6	192.7	194.8	196.8
Day 60	202.7	189.6	194.0	198.7
Day 90	193.9 Combined		196.5	197.2

Source: AUX-TG-202. Report, Table 14.3.7.3

Reviewer's comment: The sponsor offers no explanation for the difference in the baseline cholesterol values between the AA2500 subjects [higher] and the patch and placebo subjects [lower]. Likewise, no explanation is given for combining the two AA2500 groups at Day 90. In any case, no special lipid claims are made in the proposed label based on the above data.

At Day 90, the combined AA2500 group reduced the LDL-C more (118.7 mg/dL to 111.6 mg/dL) when compared to Androderm® (109.9 mg/dL to 113.5 mg/dL) and to placebo (112.5 mg/dL to 110.g mg /dL). At Day 90, the AA2500 group reduction of HDL-C (48.6 mg/dL to 44.6 mg/dL) was significant against placebo (47.1 mg/dL to 46.4 mg/dL) but not significant compared to Androderm®. With regard to serum triglycerides, there were no significant differences among the groups and no consistent pattern of increase or decreases.

Reviewer's comment: **Overall, no definitive conclusions can be drawn from this data concerning the impact of AA2500 on serum lipids.**

7.8 Hematology parameters

The results from the -202 study were consistent with results from the literature. As expected from previous studies, increases in hemoglobin and hematocrit were greater in a dose-dependent manner from the placebo group, to the testosterone patch group, to the AA2500 50 mg group and to the AA2500 100 mg group. Pooling the two AA2500 groups for Day 90 data showed a mean

change of hematocrit of 2.66%. Androderm® patch subjects, by comparison, exhibited an increase of 1.14% at Day 90. The placebo group showed a slight decrease of -0.13% at 90 days.

Hemoglobin in the AA2500 50 mg group showed a mean change over 30 and 60 days of 0.16g/dL, 0.53 g/dL, respectively. The 100 mg group was 0.34 g/dL, 0.96 g/dL respectively. Pooling the two AA2500 groups for Day 90 data showed a mean change of 0.95 g/dL. A summary of the overall incidence of clinically notable hematology parameters by treatment group is presented in sponsor Table 14, found in the original ISS.

Table 14: Incidence of Clinically Notable Hematology Parameters by Treatment Group

Parameter	AA2500 gel 50 mg N=103	AA2500 gel 100 mg N=149	Androderm 5 mg N=102	Placebo N=99	Total N=406
	%				
Hemoglobin ≥20 g/dL	0	0	0	0	0
Hematocrit ≥60%	0	0	0	1.0	0.3
RBC ≥5.9 x 10^{12}/L	6.1	6.3	1.0	1.0	4.1
Eosinophils ≥10%	2.0	0.7	2.0	0	1.3

Source Table 14.5

In the updated ISS, using the combined data from the two pivotal clinical studies and slightly lower values for hemoglobin and hematocrit, the following Table 15 is presented by the sponsor.

Table 15: Percent of Subjects Having a Clinically Notable Hematology Parameter:

Parameter	AA2500 50 mg/d (n=171)	AA2500 100 mg/d (n=221)	Patch 5 mg/d (n=170)	Placebo (n=99)	Total (n=614)
Hemoglobin ≥19 g/dL	0.6%	**2.3%**	0%	1.0%	1.2%
Hematocrit ≥58%	0.6%	**2.8%**	1.2%	1.0%	1.5%
RBC ≥5.9 x 10^{12}/L	4.9%	7.4%	1.2%	1.0%	4.4%
Eosinophils ≥10%	3.1%	1.4%	2.5%	0%	2.0%

Source: Table 14.7 (Combined AUX-TG-202 and AUX-TG-204 study data)
Note: percentages based on subjects with on-treatment values (i.e. missing values not included)

Reviewer's comment: This larger combined data shows a more definite effect of AA2500 on the production of red blood cells [compared to the testosterone patch and placebo] in a dose-dependent manner. These results are consistent with results from the medical literature.[2] Although polycythemia may occur during treatment with testosterone, hemoglobin and hematocrit levels respond well to withdrawal from treatment and return to baseline levels after discontinuation.[3] Because there may be significant increases in hemoglobin and hematocrit levels, the label should clearly state that values should be periodically monitored.

[2] Wang, C., R. S. Swedloff, et al. (2000). Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab* 85(8): 2839-53.

[3] Lund, B.C., K.A. Bever-Stille, and P.J. Perry. Testosterone and andropause: the feasibility of testosterone replacement therapy in elderly men. *Pharmacotherap* 1999. 19(8): p. 951-6.

7.9 Prostate Evaluations

The effect of AA2500 treatment on DRE results, I-PSS scores, and PSA levels was evaluated in Study -202. In the original ISS, the DRE and PSA results generated in Study -202 were also analyzed by subject age.

Digital Rectal Exam (DRE):
The frequency of No Worsening/Worsening of DRE results at the last visit was summarized by the last treatment received. This analysis was performed for all treated subjects in Study -202 and by the subsets of age and race. In summary, the number of subjects who experienced a worsening of their DRE results at the last visit was small (2.0% overall). There were no apparent differences between treatment groups with regard to worsening of DRE results from baseline to Day 90. The percentage of subjects in each treatment group whose DRE results had worsened was 3.4% and 1.4%, for the AA2500 50 mg and 100 mg groups, respectively. The subset analysis by subject age showed a possible trend toward increased incidence of worsening results with increasing age; however, the number of subjects who had a worsening of their DRE was too small to provide a meaningful analysis of this trend.

International Prostate Symptom Score (I-PSS):
The change from baseline to the last total I-PSS is summarized for all treated subjects in Table 16 below.

Table 16: Mean Changes from Baseline to Day 90 I-PSS Scores, by Last Treatment

Study Time	AA2500 gel 50 mg N=56	AA2500 gel 100 mg N=138	Androderm 5 mg N=97	Placebo N=94
	I-PSS Scores mean (SD)			
Baseline	6.21 ±5.41	5.40 ±5.70	6.10 ± 5.41	4.87 ±5.34
Day 90	6.89 ±5.93	5.26 ±5.59	5.18 ±4.47	5.29 ±5.68
Change	0.68 ±3.47	-0.14 ±3.48	-0.93 ±4.08	0.41 ±3.77

Source: Sponsor Table 14.8

Reviewer's comment: The results in the above table do not suggest an effect of AA2500 on worsening BPH. It is notable that the baseline scores were very low across treatment groups, implying a relatively asymptomatic group at baseline.

Prostate Specific Antigen:
The incidence of PSA values >4.0 ng/mL for subjects in Study AUX-202 was summarized by the last treatment received for the ATS population overall and by the subgroup age group. The last PSA value on-study was used for this analysis. The results are presented in Table 17 below.

Table 17: Overall Incidence of Subjects with PSA >4.0 ng/mL at last Treatment

	AA2500 gel 50 mg	AA2500 gel 100 mg	Androderm	Placebo	Total
Subjects (N)	103	149	102	99	406
PSA ng/mL	**Number (%) of Subjects**				
≤4.0	98.2	97.1	93.5	96.8	96.3
>4.0	1.8	2.9	6.5	3.2	3.7
Missing	47	13	10	5	28

In this analysis, a total of 14 subjects (3.7%) had a PSA value >4.0 ng/mL. The incidence of elevated PSA values in AA2500-treated subjects was lower than that of the Androderm® or placebo-treated subjects. With respect to subject age, six of the 14 subjects with PSA>4.0 ng/mL were between the ages of 46-65, eight subjects with PSA >4.0 ng/mL were in the >65 year age group, and none of the subjects in the 18-45 year group had a PSA value >4.0 ng/mL. These results are consistent with the known correlation between age and PSA level.

> **Reviewer's comment: These findings do not raise a safety issue. It is somewhat surprising that the transdermal patch, which was less effective in raising the serum testosterone levels, had at least twice the incidence of PSA > 4.0 compared to the AA2500 results. Twenty-seven subjects [evenly distributed in the 3 treatment groups] had a baseline PSA > 3 ng/dL/mL. When their baseline values were compared to final PSA values, 12 subjects had an increase and 15 had a decrease in the PSA value.**

Two cases of prostate cancer occurred during the AUX-202 study; both subjects were in the testosterone patch group. Four subjects were diagnosed with benign prostatic hyperplasia.

Sponsor conclusion:
From the results of studies AUX-202 and -204, it can be concluded that testosterone delivered by transdermal means does result in increases in PSA similar to increases cited in the literature. The magnitude of these increases in PSA, changes in I-PSS, or findings in DRE were not of concern.

> **Reviewer's comment: This reviewer agrees with the sponsor's conclusions. In other testosterone replacement studies, urine flow rate has also been measured as an evaluation of the genitourinary system. No such studies were done in the four clinical trials with AA2500. Given the relatively asymptomatic population at baseline, urine flow studies would probably not have yielded much additional information.**

7.10 Special Topics: Gel Transfer through Contact and The Effects of Washing on Treatment

Gel Transfer through Bodily Contact:
Testosterone may cause fetal abnormalities if used during pregnancy. Therefore, two Phase I safety studies (AUX-TG-206 and -209) were conducted to evaluate the potential for transfer of AA2500 gel to a second person through bodily contact.

Study -206 was designed to allow for maximum transfer of testosterone from males to females following application of a single dose of AA2500 100 mg to the male's abdomen; transfer did occur to the female. In general, the results of Study -206 showed that serum concentrations in female subjects increased during the 24 hours following skin contact with males, with the C_{max}

generally observed between 4 and 12 hours after the rubbing session. All estimates of systemic exposure and the percent change in these estimates were consistently lower for the group in which the male wore a shirt than for the groups in which the men did not wear a shirt. This indicated that introduction of a barrier to skin contact in the form of clothing appreciably reduced transfer of testosterone from males to females. This potential transfer is stated in the proposed prescribing information.

Study AUX-209 was designed to use gel application procedures consistent with the proposed labeling. This study was conducted soon after Study -206 completion and included the same investigator and almost all of the same subjects from that study.

The maximum testosterone levels in females following body-to-body contact with males who had applied testosterone gel to their shoulders and/or upper arms were below the upper limit of the normal range for healthy premenopausal females (<80 ng/dL) for all but 2 subjects. Only small increases in serum testosterone levels in females were seen when males wore a shirt. Thus, the potential for dermal transfer was greatly reduced when testosterone gel was applied to the shoulders and/or upper arms and a shirt covered the application site.

Effect of washing after dosing:
The effect of washing the AA2500 gel application site after dosing was evaluated in Study AUX-207, a Phase I, open-label, single-center study with a 4-treatment session design. A single dose of 100 mg testosterone (2 tubes of AA2500 gel) was administered topically to men in each of 4 treatment sessions, with 1 week washout between each administration. The objective of this study was to measure the effect on testosterone blood levels of washing the application site at 1 hour, 2 hours, or 6 hours after gel application.

Fifteen minutes before dosing, blood was drawn for baseline testosterone levels. At 0800 h (± 30 min) on each dosing day, subjects applied, under the direction of the investigator, two tubes of study drug to clean, dry, intact skin of the shoulders and/or upper arms. Following dosing, blood was drawn at selected intervals over a 24-hour period for determination of testosterone levels. In treatment sessions II, III, and IV, subjects washed their shoulders and/or upper arms at 1, 2, and 6 hours following dosing, respectively.

The results of this study demonstrated that washing reduces testosterone levels at all timepoints; however, when washing occurred two or more hours after application, serum testosterone levels remained within the normal range.

> Reviewer's comment: **The PK, Warnings, and Precautions sections of the label clearly reflect appropriate information about the potential for transfer of the testosterone gel and the effect of washing after dosing. Under Contraindications, it states that the gel must not be used on the abdomen or by women.**

7.11 Drug-Drug Interactions

The potential drug interactions of exogenous testosterone administration are listed in Section 6 of the NDA. Interactions between androgens and oxyphenbutazone, insulin, propranolol and corticosteroids have been documented in the literature. In Study -202, subjects who were using medications known to interfere with androgen metabolism (e.g., spironolactone, finasteride, or ketoconazole) or anabolic supplements, such as dehydroepiandrosterone (DHEA) and creatine were not permitted to enter the study. However, due to the limited absorption of topical agents, subjects who were receiving topical ketoconazole were not excluded from the study.

To evaluate the potential for drug-drug interactions with AA2500 administration, the incidence of treatment-emergent adverse events was summarized by the actual study drug treatment received at the start of the adverse event and by concomitant use of medications in selected drug classes. A subject was included in a drug class if he took a medication in the following classes at some time between the first day of study drug administration and last day of study drug administration.

- opiates
- lipid lowering agents
- antidepressants
- alpha blockers
- antihypertensive agents other than alpha blockers
- antidiabetic agents
- macrolides

The percent of subjects who experienced at least one adverse event and who had received a concomitant medication from the above drug classes is summarized by drug class and treatment groups in sponsor Table 18.

Table 18: Incidence of Adverse Events Summarized by Concomitant Drug Class and Study Treatment Group

	AA2500 Gel 50 mg	AA2500 Gel 100 mg	Testosterone Patch 5 mg	Placebo	Total
Combined (N) -202 and-204	171	221	170	99	661
Overall*	31.6%	34.4%	62.9%	40.4%	
-202 Subjects only	**103**	**149**	**102**	**99**	**406**
Drug Class			%		
Opiates	4.9	6.7	3.9	5.1	5.4
Lipid-lowering agents	8.7	11.4	16.7	13.1	12.8
Antidepressants	4.9	12.1	8.8	12.1	10.1
Alpha Blockers	5.8	8.7	6.9	4.0	6.7
Antihypertensives	12.6	22.8	31.4	17.2	22.7
Antidiabetic agents	2.9	2.0	9.8	6.1	5.4
Macrolides	0.0	1.3	0.0	0.0	0.5

*Percent of subjects with at least one AE

The highest incidence of adverse events occurred in subjects receiving antihypertensives (22.7% overall). Subjects who had received lipid-lowering agents and antidepressants reported the next highest incidence of adverse events (12.8% and 10.1%, respectively). The incidence rate for all treatment groups was comparable, suggesting there was no interaction effect of AA2500 treatment with any of the drug classes evaluated.

> Reviewer's comment: **This reviewer agrees with the sponsor's conclusion. A dose-treatment effect is apparent with AA2500 (except for anti-diabetic agents), but in several categories the placebo group actually had a higher incidence of AEs compared to AA2500. It should be kept in mind that subjects who were using medications known to interfere with androgen metabolism (e.g., spironolactone,**

finasteride, or ketoconazole) or anabolic supplements, such as dehydro-epiandrosterone (DHEA) and creatine were not permitted to enter the study.

7.12 Drug Abuse Potential and Overdose

AA2500 topical gel contains testosterone, a controlled substance in both the U.S. and Europe. Due to extensive first-pass metabolism, oral ingestion of AA2500 does not result in clinically significant serum testosterone concentrations. As of the updated ISS (cutoff date June 30, 2002 for SAEs), there have been no reports of overdose or drug abuse in the four clinical studies of the AA2500 topical gel.

Reviewer's comment: Potential for abuse of this topical formulation exists among bodybuilders, athletes, teenagers and women. The Division will help inform the public about appropriate use through clear labeling and through interaction with DDMAC in their review of product marketing.

7.13 4-Month Safety Update:
On May 6, 2002, the sponsor submitted a safety update (N-096) to the IND with an updated listing of all SAEs from the four Phase 3 clinical trials. The two open-label extension trials (-203 in the US and -208 in Europe) were ongoing at the time of the report. The information in this safety update was also submitted in the subsequent safety update, dated July 3, 2002 (see section below).

7.14 Second Safety Update:
On July 3, 2002, the sponsor submitted to the NDA an updated ISS for AA2500. The original ISS had a cutoff date of November 30, 2001, but the second ISS update has a cutoff date of March 15, 2002. It should be noted that all SAE data, regardless of study, which was received as of June 30, 2002 was included in the July 3rd updated ISS. The reviewer's analysis of safety for AA2500 is based on all the information that was submitted in the original NDA and in the ISS dated July 3, 2002. The reader is referred to the safety section of this review for details.

7.15 Labeling Issues and Revisions

The major issues in regard to labeling include [redacted] appropriate wording to allow safe use of the product, and not allowing claims specific to [redacted]. Labeling negotiations were held by several teleconferences and exchange of documents by FAX or email dating from October 22, 2002 through October 30th. Major revisions to the label were sent by the Division to the sponsor on October 28th and the final label agreed to on October 30th.

8.0 Dosing, Regimen, and Drug Administration Issues

8.1 Final Dosing Recommendation
The sponsor recommends the following:

1. Starting dose of Testim™ is 50 mg (one tube) applied once daily, preferably in the morning, to clean, dry intact skin on the shoulders and /or upper arms.
2. Morning serum testosterone levels should then be measured approximately [redacted]14 days after initiation of therapy to ensure proper serum testosterone levels are achieved.
3. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved:

The daily Testim™ dose may be increased from 50 mg (one tube) to 100 mg (two tubes) as instructed by the physician.

Reviewer's comment: **In clinical trial -202, the first time the serum testosterone level while on treatment was measured was at Day 30, and the dose adjustment was made at Day 60. This reviewer recommends that the serum testosterone level be measured approximately 14 days after 1) initiation of therapy, Furthermore, dose adjustments should NOT be made based solely on the desired clinical response. A decrease in dose may be made, however, based on an undesired clinical response (i.e., an adverse event or side effect).**

8.2 Proprietary name Testim™ 1%

The Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "Testim." The primary purpose was to determine the potential for confusion with approved proprietary and established names as well as pending names. DMETS has no objection to the use of the proprietary name. "Testim." DMETS did recommend, however, several minor labeling revisions in section III of their review to minimize potential errors with use of this topical testosterone product. These minor revisions have been noted and will be discussed with sponsor during labeling negotiations.

9.0 Use in special populations

9.1 Pediatric Waiver submission- stamp date January 18, 2002 (originally issued Jan. 16, 2002).

The sponsor requested a full waiver from requirements to test AA2500 in a pediatric population. Their reasons include:

- Testosterone has no therapeutic indication in neonates, infants, and children
- Testosterone would be unsafe to use in this population
- There is an extremely small population of pediatric patients in need of testosterone therapy for primary hypogonadism
- This formulation offers no treatment benefit over currently available therapy
- The necessary studies required to establish efficacy and safety for pediatric patients are not possible because of the small number of pediatric patients affected by conditions requiring testosterone therapy
- The label will state that the product is not to be used in patients under 18 years of age

Reviewer's comment: **The most important point made by the sponsor is the fact that "testosterone replacement" therapy is indicated rarely in children. Although there are conditions in which testosterone can help children (e.g. delayed puberty), these would represent novel indications requiring a full development program under the supervision of the metabolic and endocrine Division (DMEDP). If the sponsor wishes to develop the product for use in children, they should seek guidance from DMEDP in the future. At this time, a waiver is appropriate.**

9.2 Other Special Populations

In the four Phase III trials for AA2500, the sponsor has not studied any special populations other than adult males aged 18 to 80 with screening serum testosterone levels < 300 ng/dL. The sponsor

performed subset analyses by subject age, subject race, and etiology of the hypogonadism. These confirmed the overall efficacy of the transdermal testosterone gel.

10.0 Conclusions, Recommendations, and Labeling

10.1 Final Safety Conclusions

Exogenous testosterone has been available for decades and has been widely used and studied. In recent years, there has been renewed interest in testosterone replacement therapy, with particular emphasis on the potential for testosterone to benefit normal older men.

One testosterone gel has already been approved by the FDA for use in humans. Auxilium Pharmaceuticals Inc. evaluated the safety of its topical gel testosterone formulation (AA2500) in four Phase I studies and two Phase III trials. The majority of the safety information is derived from the completed randomized, active- and placebo-controlled, four-arm, parallel-group, multicenter, Phase III study AUX-TG-202.01R conducted in adult males with baseline testosterone levels ≤ 300 ng/dL. The four treatments under study were AA2500 50 mg testosterone gel, AA2500 100 mg testosterone gel, matching placebo gel, and Androderm® transdermal patches (2 x 2.5 mg).

In Phase I pharmacokinetic and special studies of AA2500, the incidence of adverse events was low and few events were considered to be related to the study drug. No events were considered to be serious, and there were no premature discontinuations due to adverse events. Because the potential for transfer of testosterone through bodily contact was demonstrated in two Phase I studies, the labeling for AA2500 will include precautions and recommendations to minimize that potential. A Phase I study of the effect of washing on testosterone levels concluded that in order to maintain serum testosterone levels in the normal range, the sites of application should not be washed for at least two hours after application of AA2500.

The safety of AA2500 was demonstrated in the Phase III U.S. study. The incidence of adverse events and discontinuations due to adverse events was much lower for subjects treated with AA2500 compared to those who received the Androderm patch (two 2.5 mg patches each morning). A total of 39.0% and 40.4% of subjects in the AA2500 and placebo treatment groups, respectively, experienced at least one adverse event. The incidence rate of discontinuations due to adverse events (ADOs) in the Androderm-treated subjects was much higher, due almost entirely to the number of localized skin reactions. ADOs occurred in 17.6% of the testosterone patch-treated population compared to 2.9% and 2.0% in the AA2500 gel and placebo gel groups, respectively. The incidence of SAEs was low and comparable across all treatment groups. One death was reported during the U.S. clinical studies of AA2500. A 61-year old male participating in the open-label extension study AUX-203 died because of cardiopulmonary arrest. The investigator did not believe the death was related to the AA2500 100 mg dose. This case is discussed in section 7.3 of this review (page 30).

Consistent with the class effects of testosterone supplementation, subjects treated with AA2500 experienced a Day 90 mean increase in hematocrit and hemoglobin of 2.66% and 0.95 g/dL, respectively, compared to subjects in the placebo group (–0.13% and 0.12 g/dL). However, none of the subjects treated with testosterone (AA2500 or Androderm®) reported a hematocrit or hemoglobin value outside the sponsor's clinically notable range. Fifteen subjects (5.9%) who received AA2500 exhibited a RBC of ≥5.9 x 10^{12}/L. AA2500 had no obvious detrimental effect

on total cholesterol, LDL, and HDL from their baseline values. There were no other meaningful clinical chemistry laboratory changes.

From the results of the Phase 3 USA Study AUX-202, it can be concluded that testosterone delivered by transdermal means can result in increases in PSA similar to increases cited in the literature. The magnitude of these increases in PSA, changes in I-PSS, or findings on digital rectal examination (DRE) were not felt to be clinically significant.

Before beginning androgen treatment, and yearly thereafter, patients should be evaluated by DRE and a serum PSA level. Serum HDL and LDL levels should be periodically monitored. Hemoglobin and hematocrit levels should also be checked periodically.

Subset analyses by subject age and race were performed for the purposes of the safety evaluation. With the exception of a possible age-related trend in skin irritation effects in subjects treated with Androderm®, no particular concerns were noted with respect to subject age. The analysis by subject race was rendered not meaningful by the small number of subjects who were non-Caucasian (9%).

In conclusion, the safety and tolerability of AA2500 was comparable to placebo gel and, when compared to the Androderm patch, skin irritation was less severe and much less common.

Reviewer's summary safety comments: **The exposure to AA2500 was adequate at both 90 and 180 days. Study design flaws included using an open-label transdermal patch comparator when an approved transdermal gel was available. No dose titration was used for the subjects in the transdermal patch group. Skin tolerability issues for the comparator patch are well known.**

Testosterone replacement therapy can adversely impact serum PSA, serum lipids and serum hemoglobin/hematocrit. These specific laboratory parameters should be assessed periodically during use of the product. More specific recommendations are not available at this time.

A potential dosing dilemma will be the need for an intermediary dose between 50 mg and 100 mg. Until one is available, those patients who absolutely require an intermediate dose of Testim™ will have no choice but to switch to an alternative approved product. The risk of excessive serum T levels in the 50 mg daily group was small. In order to minimize this risk, all patients will be advised to start on 50 mg daily, and all patients will be advised to have a check of their serum testosterone level approximately 14 days after starting treatment. The risk of adverse events related to excess androgen should be greatly reduced by these simple instructions.

While absolute serum DHT levels are higher with Testim™ than with Androderm®, this is likely due to an overall increased absorption of testosterone. In fact, the ratio of DHT to T is within normal range in Testim™ users.

The updated ISS, submitted July 3, 2002, and utilizing data from four Phase 3 clinical studies up to the cutoff date of March 15, 2002 (June 30, 2002 for all SAEs) is reassuring. There were no findings that, at this time, raise any new safety issues.

10.2 Recommendations on Approvability (Regulatory Action):

The reviewer recommends approval of Testim™ 1% (testosterone gel). The starting dose will be 50 mg testosterone 1% gel (1 tube), which may be titrated to 100 mg testosterone (2 tubes) based on serum levels of testosterone measured after at least 14 consecutive days of use.

10.3 Labeling Negotiations and Revisions:

Extensive labeling revisions were sent to the sponsor on October 28, 2002. All outstanding labeling issues were resolved by October 30th. The major issues in regard to labeling included [redacted] appropriate wording to allow safe use of the product, and not allowing claims [redacted]

The sponsor provided the Division with additional data from the two Phase 1 transfer studies (AUX-206 and -209), the Effect of Washing study (AUX-207), and a Hand Washing Technical Report. Analysis of this data allowed for adequate labeling concerning the issue of potential transfer of Testim™ to others [especially women and children] through direct skin contact.

Daniel Davis, M.D., M.P.H.
Medical Officer, HFD-580
Division of Reproductive and Urologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

APPENDIX:

LIST OF ABBREVIATIONS/ACRONYMS
NDA 21-454 Testim™ 1%

AA2500 (trial name of product)	Testim™ (trade name of product)
ADO(S)	discontinuation due to adverse event (s)
ATS	All treated subjects
AUX-TG 201.02	AUX-201 or -201
AUX-TG-202.01R, etc.	AUX-202 or -202, etc.
BMD	Bone mineral density
CDER	Center for Drug Evaluation and Research
CRF	Case report form
DDMAC	Division of Drug Marketing Advertising and Communication
DEXA	Dual energy x-ray absorptiometry
DHT	Dihydrotestosterone
DRE	Digital rectal exam
DRUDP	Division of Reproductive/Urology Drug Products
E_2	estradiol
FDA	Food and Drug Administration
FPL	Final printed label
IND	Investigational New Drug
IRB	institutional review board
ISE	integrated summary of efficacy
ISS	integrated summary of safety
IVRS	Interactive voice response system
MED	Male erectile dysfunction
MITT	modified intent-to-treat
MOR	medical officer review
NDA	New Drug Application
NME	new molecular entity
PD	pharmacodynamic
PK	pharmacokinetic
PSA	Prostate specific antigen
PSS	Prostate symptom score
SAE(s)	Serious adverse event(s)
T	Testosterone

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/s/

Daniel Davis
10/30/02 03:05:32 PM
MEDICAL OFFICER

Mark S. Hirsch
10/30/02 04:11:08 PM
MEDICAL OFFICER
I concur.

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