

**JOINT MEETING FOR BONE, REPRODUCTIVE
AND UROLOGIC DRUGS ADVISORY
COMMITTEE (BRUDAC)
AND THE DRUG SAFETY AND RISK
MANAGEMENT ADVISORY COMMITTEE
(DSARM AC)**

September 17, 2014

**FDA background documents for the discussion of two major
issues in testosterone replacement therapy (TRT):**

- 1. The appropriate indicated population for TRT, and**
- 2. The potential for adverse cardiovascular outcomes associated
with use of TRT**

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought two issues regarding testosterone replacement therapy (TRT) that have important public health implications to this advisory committee in order to gain the committee's insights and opinions. The first issue is identification of the appropriate patient population for whom TRT should be indicated, and the second is the potential cardiovascular risk associated with TRT. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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I. Summary Memorandum



SUMMARY MEMORANDUM

Date: August 22, 2014

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Division of Bone, Reproductive, and Urologic Products (DBRUP)

To: Advisory Committee Members
The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM AC)

Joint Advisory Committees meeting, September 17, 2014

Purpose of the Advisory Committee meeting:

The FDA is convening this joint Advisory Committee (AC) meeting to discuss two controversial issues regarding testosterone replacement therapy (TRT) that have important public health implications. The first issue is identification of the appropriate patient population for whom TRT should be indicated, and the second is the potential risk of major adverse cardiovascular events (or MACE, defined as non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death) associated with TRT use.

Regarding the appropriate patient population for TRT, the FDA will ask the AC panel to consider whether the available scientific evidence supports the benefit of testosterone treatment in the types of patients currently being prescribed testosterone in clinical practice. These considerations will be placed within the context of the clinical drug development paradigm that is currently used to support FDA approval of a TRT product.

Regarding cardiovascular safety with TRT, the FDA will ask the panel to opine on the potential risk of MACE attributable to testosterone therapy. We will also seek your advice on how best to further evaluate such cardiovascular risk should the panel determine that one exists. The panel's discussion should take into account the quality and strength of the available evidence of the CV

safety of TRT products in determining drug attribution and whether there are sub-populations of TRT users who may be at higher risk for adverse CV outcomes.

In addition to the briefing documents, there will be several presentations over the course of the day to provide the AC members with the necessary background information for their deliberations. First, two experts will provide their perspectives on the scientific evidence that bears on the appropriate indicated population for testosterone therapy. Several testosterone sponsors have chosen to collaborate on a joint presentation that will provide their perspectives on the appropriate indicated population for TRT and the potential for cardiovascular risk associated with this use. The sponsor presentation will be followed by several FDA presentations that will cover the following topics:

- Drug utilization data for TRT examining recent trends
- Direct-to-consumer promotional materials
- The clinical development paradigm for FDA approval of a TRT product, and the current FDA-approved indication for TRT
- FDA assessment of cardiovascular risk in men prescribed testosterone therapy

Following all the presentations, the AC panel members will be asked to consider several discussion points before the voting questions.

We look forward to a thorough and reasoned discussion of these complex, important matters. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

Background:

This section provides a brief summary of FDA's rationale for bringing issues regarding TRT to a joint meeting of the BRUDAC and the DSaRM AC. More detailed information is included in the accompanying memoranda prepared by staff within FDA's Office of New Drugs, Office of Surveillance and Epidemiology, Office of Biostatistics, and Office of Prescription Drug Promotion.

Users of TRT: Testosterone has been approved in the United States since the 1950s as replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. Androgens, including testosterone, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis and scrotum and the development of male hair distribution, laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. In men, the hypothalamus and pituitary regulate testosterone production by the testes. Therefore, a deficiency or absence of endogenous testosterone can occur with testicular conditions (examples include testicular damage due to chemotherapy, genetic or congenital testicular abnormalities) or with hypothalamic or pituitary conditions (examples include damage from a pituitary tumor, pituitary surgery or pituitary irradiation). Serum testosterone concentrations can be replaced satisfactorily regardless of whether the testosterone deficiency is due to testicular conditions (so called primary

hypogonadism) or hypothalamic/pituitary conditions (so called secondary hypogonadism). Because the intended use of testosterone is ‘replacement therapy,’ the FDA has only required that an investigational testosterone treatment demonstrate acceptable restoration of serum testosterone concentrations to the normal range to gain FDA approval. This approach is reasonable for patients with ‘classic’ hypogonadism (i.e., those who have an absence or deficiency of testosterone due to documented testicular or hypothalamic/pituitary disease). In these patients, replacing testosterone is necessary for the development or maintenance of secondary sexual characteristics.

A more controversial treatment population is aging men who have low serum testosterone concentrations for no apparent reason other than age, and who experience non-specific symptoms of aging that overlap with those of classic hypogonadism. Serum concentrations of testosterone decrease as men age. This decline is usually modest but testosterone concentrations can fall below the lower limit of the normal range for younger, healthy men. This phenomenon is sometimes referred to as ‘andropause’ or ‘age-related hypogonadism.’ The Baltimore Longitudinal Study of Aging reported that the percentage of study subjects with total testosterone concentrations in the hypogonadal range (the study defined this range as total testosterone <325 ng/dL) was 20, 30, and 50 percent for men in their 60s, 70s, and 80s, respectively.¹ Furthermore, aging men often experience many of the signs and symptoms that are associated with hypogonadism, including decreases in energy level, sexual function, bone mineral density, muscle mass and strength, and increases in fat mass. Whether these symptoms are a clinical consequence of the age-related decline in endogenous testosterone has not been established, and therefore, the need to replace testosterone in these older men remains debatable.

FDA’s analysis of drug utilization data for TRT over the past 5 years shows a significant increase in the use of testosterone therapy. From 2009 to 2013, sales of TRT in terms of kilograms of active ingredient saw an increase of 65%, with approximately 8,500 kilograms sold in 2009 to 14,000 kilograms sold in 2013. In 2010, 1.3 million patients received a prescription for testosterone and by 2013, this number has risen to 2.3 million patients. Direct-to-consumer advertisement emphasizing the benefits of TRT related to quality-of-life, such as vitality and strength, and non-branded disease awareness campaigns of ‘low T’ have targeted a broad population of men. According to a recent report² using data from commercial health insurance claims, the largest group of patients prescribed TRT is men 40 to 60 years of age. FDA’s drug utilization analysis corroborated this observation, with men 40 to 64 years of age accounting for approximately 70% of men prescribed TRT. FDA analysis also showed the age group of men 40 to 64 years of age had the largest relative increase in TRT prescriptions, from approximately 850,000 to 1.5 million patients, from 2010 to 2013. In the same report, only about one-half of men taking testosterone therapy had been diagnosed with hypogonadism, and 25% did not have evidence of having their testosterone concentrations tested prior to initiating therapy. FDA’s analysis revealed that 21% of patients prescribed TRT did not have evidence of laboratory testing for serum testosterone concentrations at any time during TRT treatment, including testing prior to the first TRT prescription. This is particularly concerning because the diagnosis of hypogonadism requires documented evidence of low or absent serum testosterone concentrations and the

¹ Harman SM, et al. Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab.* 2001; 86(2):724.

² Baillargeon J, et al.. Research Letter: Trends in Androgen Prescribing in the United States. *JAMA Internal Medicine* 2013; 173(15): 1465-1466.

appropriate TRT dose cannot be determined without following serum testosterone concentrations on therapy. The increased use of testosterone in older men indicate that TRT use has expanded significantly and appears to include those considered to have ‘age-related hypogonadism,’ asymptomatic individuals with low serum testosterone concentrations, and symptomatic men with normal or unknown serum testosterone concentrations. As mentioned previously, treatment benefits with TRT for ‘age-related hypogonadism’ remain questionable, and there are no reliable data on the benefit in such a population.

Based on the above considerations, the FDA has decided to reassess the appropriate patient population for TRT and to ensure that the labeling for FDA-approved testosterone therapies appropriately reflects the population for whom TRT is indicated.

Cardiovascular safety with TRT: It is within the current context of the expanded use of testosterone that recent publications have reported a potential for an increased risk of CV-related outcomes in men prescribed TRT. In 2010, the FDA began an investigation of the CV safety of approved testosterone products after a small, placebo-controlled testosterone trial in elderly men was discontinued prematurely.³ This trial reported an overall increase in various cardiovascular adverse events with testosterone treatment. After a thorough review of these study results and other available published literature, the FDA determined that there was insufficient evidence to conclude that testosterone therapy in older men was associated with an increased risk of adverse CV outcomes. Recently, the FDA decided to reassess the potential risk of adverse CV outcomes associated with testosterone therapy after new observational studies were published (see the FDA Drug Safety Communication published January 31, 2014, available at <http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm>). The first new observational study² included men who were undergoing coronary angiography for the assessment of coronary artery disease and who had low serum testosterone. Some of the men received testosterone treatment while others did not. This study suggested an approximately 30 percent increased risk of adverse cardiovascular events in the group that had been prescribed testosterone therapy. A second recent observational study⁴ reported an increased risk of myocardial infarction in older men, as well as in younger men with pre-existing heart disease, who filled a prescription for testosterone therapy. The study reported a two-fold increase in the risk of myocardial infarction among men aged 65 years and older in the first 90 days following the first prescription. Among men less than 65 years of age with a preexisting history of heart disease, the study reported a two- to three-fold increased risk of myocardial infarction in the first 90 days following a first prescription. In contrast, two other observational studies in men with a mean age of approximately 60 years reported a significant reduction in all-cause mortality associated with TRT therapy.^{5,6}

Because of important limitations, the available epidemiological studies do not provide convincing evidence that TRT is associated with adverse CV outcomes. In addition to the observational studies mentioned above, there are some published controlled trials but these controlled trials are limited by small sample size, lack of pre-defined and adequately adjudicated CV outcomes, short duration of treatment and follow-up, and heterogeneous study populations.

³ Basaria, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363(2):109-122.

⁴ Finkle WD, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS ONE. 2014; 9(1): e85805.

⁵ Shores, M, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab. 2012; 97(6):2050-2058.

⁶ Muraleedharan, V, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement therapy improves survival in men with type 2 diabetes. European Journal of Endocrinology. 2013;169:725-733.

Given these limitations of the available data and the conflicting study results, the FDA has decided to seek AC input on the potential risk of MACE attributable to testosterone therapy and how best to further evaluate such cardiovascular risk, should the AC panel determine that one exists.

Topics for Discussion:

1. a. The current approach to establishing the efficacy and safety of testosterone products for marketing approval is based upon pharmacokinetic assessments of serum testosterone concentrations and an acceptable safety profile. The product must be able to reliably raise low serum testosterone concentrations into the normal range for young, healthy men. FDA does not require a demonstration that testosterone products ameliorate or improve any specific hypogonadal sign or symptom. Describe the populations for which approval would be supported based on data generated from this current approach.
- b. Discuss what changes, if any, would be needed to the current clinical development paradigm to support an indication for TRT in men with “age-related” hypogonadism.
2. Discuss whether the totality of the data indicates a cardiovascular safety signal associated with the use of testosterone therapy. Include in your discussion:
 - a. The strength of the signal
 - b. The biologic plausibility of the signal
 - c. Whether you believe there is a signal that is restricted to a certain subset of the population using testosterone products or whether there is a signal that applies to all users.
 - d. Whether the evidence on major adverse cardiovascular events associated with TRT is sufficiently informative to warrant inclusion of such information in labeling.
3. The current indication for TRT is:

“DRUG X is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone”

- *Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.*
- *Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.”*

Should the FDA revise the current indication for testosterone therapies?

Provide a rationale for your vote. If you vote to change the indication, describe the specific changes you are recommending to the indication statement.

4. Should FDA require sponsors of testosterone products to conduct a postmarketing study (e.g. observational study, controlled clinical trial) to further assess a potential cardiovascular risk with the use of TRT?
 - a. No, a postmarket study should not be required
 - b. Yes, but only if TRT is also approved for age-related hypogonadism
 - c. Yes, regardless of the indication for testosterone therapy

Provide a rationale for your answer. If you vote yes, discuss the type of study that should be required (e.g., observational study, controlled clinical trial). Include a discussion of the study population that should be enrolled as well as an acceptable degree of risk that would need to be excluded.

**II. Clinical Background
Document –
Office of Drug Evaluation III,
Division of Bone,
Reproductive and Urologic
Products**

Advisory Committee

Clinical Background Document

**Testosterone Replacement Therapy:
Clinical Development and Target Population**

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1. Introduction: Testosterone Replacement Therapy

Endogenous androgens, including testosterone (T) and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs, and for the maintenance of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations in association with accompanying signs and symptoms, such as decreased sexual desire, regression of secondary sexual characteristics, fatigue, changes in mood, changes in body fat and lean body mass, and osteoporosis.

Low or absent serum testosterone concentrations due to hypogonadism can be successfully restored with exogenous testosterone therapy. Testosterone therapy is currently available in the United States in a number of formulations, including: topical gels (for example, AndroGel 1%, AndroGel 1.62%, Testim, Fortesta, and others), a topical solution (Axiron), a transdermal system (Androderm), a buccal system (Striant), an intranasal gel (Natesto), intramuscular injections (testosterone enanthate, testosterone cypionate, and testosterone undecanoate), oral methyltestosterone, and subcutaneously implanted pellets (Testopel).

Topical testosterone products are currently the most widely used testosterone replacement therapies (TRT).

2. Studies Supporting Approval of a New Drug Application (NDA) for Testosterone Replacement Therapy

To support approval of a testosterone product for TRT, the FDA has required evidence that the testosterone product is safe for use in hypogonadal adult males, and that the product reliably increases deficient serum T concentrations to the normal range for eugonadal males (to serum T concentrations that are observed in healthy, young men). FDA has not required a demonstration in Phase 3 TRT studies that testosterone ameliorates or improves any specific hypogonadal sign or symptom. Thus, for testosterone products for the TRT indication, the FDA-required efficacy testing is based upon pharmacokinetic assessments of serum T concentrations and not based upon clinical efficacy parameters.

The current class indication for testosterone products for TRT is the following:

“X is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone”

- *Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.*
- *Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or pituitary-hypothalamic injury from*

tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.”

In meeting the FDA safety and efficacy requirements for the TRT indication, Sponsors of testosterone products typically provide: 1) data from Phase 1 and 2 studies that investigate single- and multiple-dose pharmacokinetics, dose-exposure response, and preliminary safety and tolerability; and 2) substantial data from one or more Phase 3 studies that investigate the efficacy and safety of the testosterone product for the intended to-be-marketed use as TRT.

Additional human studies may also be required by the FDA for testosterone products, based on the individual clinical situation. For example, in the case of topically applied testosterone products, the FDA has typically required evidence of skin safety based on periodic skin application site assessments in Phase 3 clinical studies, as well as evidence from Phase 1 studies that investigate the potential for secondary exposure to non-users. Other such studies in TRT applications have included, but are not limited to:

- Studies to assess skin sensitization and skin irritation of a topically applied product
- Studies to assess the effect of skin washing on systemic exposure from a topically applied product
- Studies to assess the effect of concomitantly administered topical products, such as sunscreen, for a topically applied product
- Studies to assess the effect of differing skin application sites on systemic exposure for a topically administered product

2.1 Phase 3 Studies of Testosterone Replacement Therapy in NDAs

2.2.1 Phase 3 TRT Study Designs

The bulk of clinical efficacy and safety data in a new drug application for TRT come from one or more multi-center, Phase 3 studies. For the standard class indication for TRT, a single Phase 3 study with supportive evidence from Phase 1 and 2 studies is an acceptable drug development program strategy.

The Phase 3 study of a new testosterone product for TRT is generally designed as an open-label, single-arm clinical trial that typically has three treatment periods, including: 1) a dose-finding (or dose-titration) period, 2) a “stable dose” period, and 3) a safety “extension” period. The duration of these three study periods may vary, but the dose titration and “stable dose” periods are typically 6-8 weeks each (e.g., 12-16 weeks in duration when combined), and the safety extension period is typically 12 to 36 weeks in duration. Overall, a study treatment duration of 24 to 52 weeks is considered a reasonable assessment of safety for a testosterone product for the standard class indication for TRT.

Of note, the duration of the initial dose-titration phase may vary based upon the number of available dose strengths, as well as the time to reach steady state serum T concentrations for the individual product.

Further, the scenario described here is generally applicable to a testosterone product that is applied or taken on a daily basis, or applied or taken more than once per day. For testosterone products with a longer dosing interval; for example, intramuscular depot injections, there may be only one or two dose strengths tested in Phase 3 studies, there may be no dose-titration period (rather, fixed doses may be tested in parallel groups), and the Phase 3 studies for such products usually have longer treatment durations, depending on the dosing interval for the individual product and the number of doses required to reach steady state serum T concentrations.

With this basic study design framework in mind, it is important to realize that designs for Phase 3 TRT studies have varied, with some Sponsors having conducted randomized and blinded, placebo- and active-controlled trials (RCTs) of testosterone products to achieve the same standard class indication for TRT. However, such RCTs are less frequently conducted in the development of testosterone products for TRT than are the more typical, open-label, single-arm, uncontrolled, dose-titration design studies.

2.2.2 Phase 3 TRT Study Subjects

This section will touch upon the number of subjects who participate in typical Phase 3 TRT studies, as well as the subject characteristics typically required for study eligibility.

The number of subjects enrolled in Phase 3 TRT studies varies as a consequence of study design, and product-specific situations. In a typical, open-label, uncontrolled, Phase 3 study for a testosterone product, approximately one hundred (100) to several hundred adult men have been included to collect sufficient data on clinical and laboratory safety, as well as to confirm the adequacy of T replacement within the normal range.

In these Phase 3 studies, key eligibility criteria include, but are not limited to the following:

Inclusion Criteria

- Males, at least 18 years of age (some TRT studies have an upper age limit, for example, 65 years of age)
- A diagnosis of primary hypogonadism (congenital or acquired) - e.g., testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals, etc., **or**:

A diagnosis of secondary (hypogonadotropic) hypogonadism (congenital or acquired) - e.g., idiopathic gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumors, trauma or radiation, etc.

- Average morning serum total T concentration below the normal range for healthy eugonadal adult males as determined by two laboratory specimens, usually collected on two separate days. While this lower level of normal has frequently been set as <300 ng/dL for the purposes of the clinical studies, the lower level of normal for healthy,

eugonadal males should not be misunderstood to be a single, universally accepted cut-off threshold for abnormally low serum testosterone concentration.

- Naïve to androgen replacement; or has undergone washout of at least 12 weeks following intramuscular androgen injections, four weeks following topical or buccal androgens, or 3 weeks following oral androgens.
- No significant underlying medical condition that would be adversely impacted by testosterone replacement.

Exclusion Criteria

- Serum testosterone concentration <300 ng/dL secondary to causes other than primary or secondary hypogonadism.
- Past, current, or suspected prostate or breast cancer.
- International Prostate Symptom Score (IPSS) above a pre-defined threshold (e.g., >15 points), that reflects clinically meaningful benign prostatic hypertrophy (BPH) symptoms.
- Abnormal prostate finding on digital rectal examination.
- Serum prostate specific antigen (PSA) above a pre-defined, clinically meaningful threshold (e.g., > 2.5 ng/mL, > 4.0 ng/mL, etc.). In some Phase 3 TRT trials, a subject may be excluded with a “borderline” clinically meaningful abnormal serum PSA (e.g., 2.6 - 3.7 ng/mL) unless a prostate biopsy has ruled out prostate cancer within 6 months of the Screening visit.
- Excessively low or excessively high body mass index (BMI) (e.g., < 18 or > 40 kg/m²).
- Subject is currently seeking to father a child or is seeking fertility within one year of trial participation.
- Presence of poorly-controlled diabetes mellitus.
- History or current obstructive sleep apnea.
- Clinically significant co-morbid conditions that would interfere with the subject’s participation or compromise the subject’s safety.
- Excessively high hemoglobin (e.g., >16.0 g/dL) or hematocrit (e.g., >48%).

It should be noted that this is an abbreviated listing of the overall eligibility criteria in Phase 3 TRT studies, intended as a brief overview and to contribute to the larger discussion of eligibility for TRT trials and TRT itself.

It is important to note that in the majority of subjects in Phase 3 TRT trials, a specific etiology for the diagnosis of hypogonadism has not been determined (idiopathic hypogonadism), and perhaps most of these subjects have this condition as a consequence of normal aging. For other Phase 3 TRT trial subjects with idiopathic hypogonadism, the underlying etiology may be obesity-related, due at least in part to excess aromatase activity in fat tissues, resulting in estrogen-related suppression of the hypothalamic-pituitary axis. Inclusion of such patients into these Phase 3 trials facilitates enrollment and improves trial feasibility because these patients are more common than those who have a specific underlying etiology for their hypogonadism. In addition, such trials establish efficacy by showing an increase in serum T to the normal range, an

efficacy endpoint that should not be significantly impacted by the underlying etiology for the low serum T.

It is critical to understand that despite the majority of study subjects lacking a specific etiology for their hypogonadism, with a large percentage likely reflecting hypogonadism associated with normal aging or obesity, the standard class TRT indication does not include “normal aging” or “obesity” as an etiology. To date, no Sponsor has submitted a new drug application seeking specific approval for such indications.

2.2.3 Phase 3 TRT Efficacy Endpoints

As previously noted, for testosterone products for the TRT indication, FDA requires efficacy testing based upon pharmacokinetic assessments of serum testosterone concentrations, and not based upon clinical efficacy parameters. Testosterone products for TRT must demonstrate that they successfully restore serum testosterone to within the normal range for healthy, eugonadal males. To meet this requirement, the product must achieve success in Phase 3 TRT studies on the primary and critical secondary efficacy endpoints, as follows:

The primary efficacy endpoint is the percentage of subjects with an average serum testosterone concentration (Cavg) within the normal range following completion of all dose-titration (if titration is part of the regimen), and while on a stable testosterone dose at steady-state exposure.

The average serum T concentration is a time-averaged calculation, whereby total exposure using area-under-the-(concentration-time) curve (AUC) is divided by the measurement time interval; for example, divided by 24 hours when pharmacokinetic samples are obtained over a 24 period for a product that is used daily or more than once daily.

A “normal” Cavg range is intended to reflect the serum T concentrations in healthy, eugonadal, adult males. In Phase 3 TRT trials, in general, the lower concentration limit of normal for Cavg has been 300 ng/dL; and the upper concentration limit of normal for Cavg has been 1000 ng/dL, 1050 ng/dL, or 1100 ng/dL.

While these concentration limits for “normal” Cavg have been used in Phase 3 TRT trials in support of approval of testosterone product new drug applications, it should not be misunderstood that these are universally accepted lower and upper serum T Cavg concentration limits.

Success for the primary Cavg endpoint in Phase 3 TRT trials requires that at least 75% of subjects on active treatment achieve a Cavg within the normal range, which is often set as 300 to 1000 ng/dL (or 1050 ng/dL, or 1100 ng/dL, as discussed above); and that the lower bound of the 95% confidence interval achieved for this result must not be less than 65%.

In addition to the primary endpoint (Cavg “responders”), FDA requires success on a critical secondary efficacy endpoint that is intended to limit the maximum serum concentrations associated with a testosterone product for TRT (referred to as Cmax “outliers”).

Based on an upper limit for C_{avg} of 1000 ng/dL (or 1050 ng/dL, or 1100 ng/dL), FDA has used three criteria for demonstration of acceptable limitations on C_{max} outliers, as follows:

- C_{max} ≤1500 ng/dL in at least 85% of subjects
- C_{max} between 1800 and 2500 ng/dL in not more than 5% of subjects
- C_{max} >2500 ng/dL in no subject

In addition to the primary and critical secondary T-related endpoints, FDA requires that Phase 3 TRT trials also collect information on the primary metabolites of testosterone, dihydrotestosterone (DHT) and estradiol (E2), which are important hormone parameters in their own right. Pharmacokinetic data for these metabolites are assessed in standard fashion to report serum concentrations, as well as to report parent:metabolite ratios (e.g., T to DHT and T to E2).

In general, Sponsors also measure follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in order to provide further evidence of the androgenic effect of the testosterone product, in regard to feedback on the hypothalamic-pituitary-gonadal axis.

Other hormone concentrations and related analytes that might be evaluated include: sex hormone binding globulin (SHBG) and free testosterone.

In addition to serum hormone concentrations, Phase 3 TRT trials have typically incorporated clinical efficacy parameters as either secondary or exploratory endpoints. These parameters have included measures of sexual desire/libido and erectile function, frequency of sexual activity, aspects of negative and positive mood, overall and disease-specific quality of life, indices of body composition (fat mass and lean body mass), and bone mineral density. When such measures are evaluated in Phase 3 TRT studies and reported in new drug applications for testosterone products, FDA reviews these data for clinically appropriate trends; for example, observed improvement from baseline in sexual desire/libido, sexual activity frequency, and erectile function; enhanced positive and diminished negative aspects of mood; reduced body fat and increased lean body mass; and increased bone mineral density. The effect of drug treatment, however, on these efficacy outcomes often remains inconclusive because many Phase 3 TRT trials are uncontrolled and open-label. Furthermore, these endpoints are often not measured by scientifically sound methodologies required for labeling claims.

In summary, FDA currently requires evidence that the testosterone product is safe for use in hypogonadal adult males, and that the product reliably raises serum testosterone concentrations to concentrations that are within the normal range for healthy, eugonadal males. FDA has *not* required a demonstration in Phase 3 studies that testosterone products ameliorate or improve any specific hypogonadal sign or symptom. Thus, for testosterone products for the TRT indication, the FDA-required efficacy testing is based upon pharmacokinetic assessments of serum testosterone concentrations, not based upon clinical efficacy parameters.

3. Premise for the Current Regulatory Paradigm and Challenges

3.1 Premise for the Current Regulatory Paradigm

The information provided in Section 2 of this memorandum outlines the current paradigm for overall and Phase 3 clinical investigation of a testosterone product for TRT to support a new drug application for marketing approval.

The current regulatory paradigm is based upon the premise that testosterone products are approved as replacement therapy, specifically indicated to “replace” testosterone in adult males with specific conditions associated with absent or deficient endogenous testosterone. The specific “*associated conditions*” that are listed in the currently approved indication (see Section 2 of this memorandum) include clear etiologies for hypogonadism, such as: 1) testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals; and 2) hypogonadotropic hypogonadism due to pituitary-hypothalamic injury from tumors, trauma, or radiation.

Based on the specific wording of the current class indication for testosterone products for TRT, the target population for TRT (other than those with ‘idiopathic’ hypogonadism, which is discussed below) would appear to be generally well-recognized, quite clear, and specific (e.g., Klinefelter’s syndrome, toxic damage, pituitary injury). In adult hypogonadal men with such clear etiologies for their hypogonadism, replacement of absent or deficient endogenous testosterone to within the normal, eugonadal range has been a long-standing, well-accepted method of disease management. Therefore, the existing regulatory paradigm for TRT that requires restoration of deficient endogenous testosterone to within the “normal range” and an acceptable safety profile is a reasonable approach. In this population with ‘classic’ hypogonadism, the need to evaluate clinical endpoints in phase 3 studies, beyond the current regulatory paradigm, does not appear to be necessary to establish the efficacy and safety of a testosterone replacement product.

3.3 *Challenges within the Current Regulatory Paradigm*

Challenges within the current regulatory paradigm arise when considering the use of testosterone for idiopathic hypogonadism, particularly in aging men. In this population, the etiology for low serum testosterone concentrations and clinical signs and symptoms (e.g., sexual desire, mood, energy, fatigue, etc.) may both be related to normal aging or to an underlying disease, such as obesity. It is not known whether replacing serum testosterone concentrations in these men to the normal range for young, healthy men has a direct clinical benefit. Accordingly it would appear judicious and clinically appropriate to have efficacy data from valid clinical endpoints, demonstrating meaningful clinical benefit with testosterone in this population. For idiopathic hypogonadism, particularly in aging men, the existing regulatory paradigm may need re-consideration with regard to how safety and efficacy for testosterone products should be demonstrated. However, a number of challenges hinder the incorporation of such clinical efficacy parameters into Phase 3 trials. First, it is unclear whether the accompanying clinical signs and symptoms in this population are caused by a deficiency or absence of endogenous testosterone, or whether these signs and symptoms are linked to some other co-morbidities, or to normal aging itself. Such clinical conditions include, but are not limited to changes in sexual

desire, frequency of sexual activity, erectile function, mood, energy, overall quality of life, body composition (lean and fat body mass), and bone mineral density. This list encompasses potential clinical conditions that have been associated with hypogonadism or with other diseases or aging. Second, should it eventually become possible to determine which clinical conditions are due to low serum testosterone in an “idiopathic” hypogonadal population like the aging male, there remains the issue of selecting valid, reliable relevant clinical endpoints for studies assessing the effect of testosterone on those specific conditions. And lastly, should it become possible to select these clinical endpoints, there then remains the challenge of defining clinically meaningful changes for those endpoints.

4. Summary

There appears to be at least two major challenges in the current regulatory paradigm for a testosterone product. These challenges relate to labeling and safety and efficacy testing paradigms for the “idiopathic” hypogonadal population, particularly in aging men:

- First, although the label currently lists a number of very clear etiologies of male hypogonadism (e.g., Klinefelter’s syndrome, toxic damage, etc.), it does not clearly differentiate between etiologies that are sufficiently clear and well-defined (“classic” hypogonadism) to support use of TRT under the current regulatory paradigm vs. etiologies that are vague and less well-defined (“idiopathic”, or “age-related”) where “hypogonadal” signs and symptoms might be a consequence of other co-morbid conditions or of aging itself.
- Second, the safety and efficacy testing strategy for the “idiopathic” populations, particularly in aging men, is yet to be determined; for example, the study designs, endpoints, durations and sample sizes that would be needed to support the specific approval of testosterone products in this less well-defined population require additional consideration, discussion, and perhaps additional information prior to study planning.

III. Memorandum - Office of Surveillance and Epidemiology, Division of Epidemiology II

a. Introductory Memorandum: Epidemiology

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

INTRODUCTION MEMORANDUM: EPIDEMIOLOGY

Date: August 12, 2014

From: David Moeny, R.Ph., M.P.H., Epidemiologist Team Leader
Division of Epidemiology II, OSE

Judy Staffa, Ph.D., R.Ph., Director
Division of Epidemiology II, OSE

To: Advisory Committee Members
The Bone, Reproductive and Urologic Drugs Advisory
Committee (BRUDAC) and the Drug Safety and Risk
Management Advisory Committee (DSaRM AC)

Joint Advisory Committees meeting, September 17, 2014

Background and Introduction

In 2010, the Division of Reproductive and Urologic Products (DRUP, now the Division of Bone, Reproductive and Urologic Products or DBRUP) opened a Tracked Safety Issue (TSI)¹, initiating a review of the safety of testosterone replacement therapy (TRT) products. The TSI was initiated because the clinical trial, the Testosterone in Older Men with Mobility Limitations (TOM) Trial, was stopped early due to an imbalance of cardiovascular-related adverse events in the testosterone gel arm compared to placebo. At that time, DBRUP also conducted a literature search, identifying two meta-analyses and one systematic qualitative review that evaluated the risk of adverse cardiovascular (CV) events associated with testosterone replacement therapy. DBRUP requested that the Division of Epidemiology (DEPI) review and provide comments on these articles. After review of the meta-analyses and systematic review, along with their constituent studies, DEPI concluded that the studies did not demonstrate that TRT is associated with an increased risk of CV events. Further, DEPI noted that there was a general trend towards improved lipid profiles, with the potential to decrease the risk of adverse CV events. In January, 2011, after weighing all available evidence, the FDA closed the TSI indicating that there was insufficient evidence of a cardiovascular risk associated with TRT to warrant a regulatory action.

The TSI was reopened in December 2013 after the publication of an observational study by Vigen et al. that reported an increased risk of cardiovascular adverse events associated with testosterone therapy. In January 2014, Finkle et al. published a study that also reported an increased CV risk with testosterone therapy. In addition, a meta-analysis of placebo-controlled trials (Xu, Freeman, Cowling, & Schooling, December 2013) reported that testosterone therapy was associated with an increased risk of adverse CV events.

To evaluate the safety signal from these three new studies, and to provide background and context for this advisory committee meeting, DEPI has provided the following reviews:

- An analysis of TRT drug utilization, consisting of examining the nationwide use trends, concurrency with other cardiovascular drug products, and duration of use
- An epidemiologic review of the Xu meta-analysis of placebo-controlled trials
- A literature search to identify additional observational studies, and in conjunction with the Division of Biometrics 7 (DB7), a review of these studies as well as the Finkle and Vigen studies.

¹ A Tracked Safety Issue (TSI) refers to the tracking of activities implemented when FDA investigates significant safety issues associated with marketed drugs that require input from several FDA Divisions, Offices, another FDA Center, and/or that require a regulatory briefing, Drug Safety Oversight Board meeting, or advisory committee meeting for their evaluation

Drug utilization

Drug use data obtained by FDA demonstrated that there has been an increase in the use of testosterone drug products in the U.S. over the most recent 5 years. Wholesale sales, in terms of kilograms of active ingredient, rose from 8,453 kg sold in 2009 to 14,023 kg sold in 2013. By dosage form, topical and injectable products accounted for the largest share of products sold over these 5 years, with approximately 71% and 24% of sales, respectively. The largest relative increase was seen in injectable testosterone products, whose distribution approximately doubled over the period examined. The distribution of topical products increased by a lesser amount, roughly 53% over the same period. Between 2010 and 2013, the number of patients receiving a testosterone prescription through US retail pharmacies rose from 1.3 million patients to 2.3 million patients, an increase of 76%. For example, men between the ages of 40-64 years accounted for the largest portion of these 2.3 million patients in 2013 (69%), followed by men aged 65-74 years with 14%. Men between the ages 40-64 years accounted for the largest increase in the absolute number of patients from approximately 844,000 patients in 2010 to 1.5 million patients in 2013, (increase of approximately 657,000, 78% relative increase), followed by increases of approximately 149,000 among men aged less than 39 years (a 99% increase) and 119,000 for men age 65-74 years (a 65% increase). According to U.S. office-based physician practices survey data, "Other Testicular Hypofunction" (ICD-9 257.2) was the most common diagnosis associated with the use of testosterone products in male patients.

Existing cardiovascular (CV) disease appeared to be a potential confounder or risk modifier in the observational studies evaluating testosterone treatment and adverse CV outcomes. To evaluate the extent of this issue in real-world use of testosterone, we determined the proportion of patients receiving testosterone prescriptions concurrently with a prescription for cardiovascular medication. Utilizing nationally projected data capturing outpatient retail prescriptions, we determined that during 2013, out of the approximately 2.3 million patients who received a testosterone prescription, approximately 1.3 million patients also had a concurrent claim for at least one cardiovascular medication; this represents approximately 57% of patients who received a prescription for testosterone product.

Finally, DEPI examined the proportion of patients with evidence of serum testosterone concentration testing prior to initiation of testosterone therapy and analyzed the duration of testosterone use. Using data capturing healthcare transactions among a commercially insured population, we identified incident users of testosterone therapy after January 1, 2008 (n=243,091), and determined that approximately 72% had evidence of laboratory testing for testosterone levels prior to their first testosterone prescription. In this population, users who initiated therapy after 2008 had a median treatment duration of 96 days of therapy (interquartile range 34, 240 days) and a mean treatment duration of 187 days (standard deviation 229).

Comments

Our analysis showed that TRT use is increasing, and that TRT is used predominantly by men who are between the ages of 40-64 years, followed by those age 65 to 74 years. The diagnosis most commonly associated with TRT drug use mentions, and in fact often the only diagnosis mentioned, is “Testicular hypofunction NEC”. The non-specificity of this hypogonadal diagnosis coupled with the increase in the use across all age groups, makes it unclear what criteria clinicians may be using for prescribing TRT.

In DEPI’s evaluation of a study population of commercially insured patients, testing for testosterone level before the first TRT prescription claim occurred in 72% of the patients. Furthermore, 6% of the total sample population had a claim for testosterone testing only after the initiation of the first TRT prescription. Approximately 21% of the study patients did not have a claim for a testosterone level test captured during the study period. It is unclear whether this indicates patients initiate therapy without testing, whether testing occurred but a claim was not captured, or whether this is reflective of other changes in prescribing criteria.

Xu Meta-analysis

DEPI evaluated a meta-analysis of placebo-controlled trials (Xu et al., 2013) and four additional files that accompanied the original study, as well as each individual component randomized, placebo-controlled trial (RCT).

Combining the results of 27 published RCTs representing 2,994 men and 180 cardiovascular-related events (CREs), Xu et al. found that testosterone therapy was associated with an increased odds of a CRE (OR 1.5, 95% CI 1.1, 2.1; trim and fill OR 1.7, 95% CI 1.2, 2.4) when compared to placebo. When the analysis was restricted to serious CREs, the estimate was similar. The effect of testosterone therapy varied with source of funding (p-value for interaction 0.03). In non-industry funded trials, the odds ratio was increased (OR 2.1, 95% CI 1.3, 3.2) while in pharmaceutical industry-funded trials (OR 0.9, 95% CI 0.5 to 1.6), it was not.

Comments

Limitations of the study include inconsistent and incomplete reporting of adverse events, substantial clinical heterogeneity in the design and conduct of the trials as well as in the types of cardiovascular outcomes reported, potential bias resulting from selection of component trials, and variable quality of the trials, particularly with regard to ascertainment of cardiovascular safety outcomes. The noted discrepancy in CRE risk based on funding source, while interesting, was not a pre-specified analysis. The observed difference may have been due to chance or to differences in study design or adverse event reporting.

Although the Xu meta-analysis was carefully conducted and the paper well-written, DEPI concludes that, because of substantial methodological limitations, this study does not provide conclusive evidence of a causal association between testosterone therapy and cardiovascular events.

SUMMARY OF OBSERVATIONAL STUDIES

DEPI conducted a literature search to identify observational studies that examined the risk of CV events in association with TRT, and identified 5 studies for review (Shores et al. 2012, Muraleedharan et al. 2013, Vigen et al, 2013, Finkle et al. 2014, and Baillargeon et al. 2014). DEPI, in collaboration with the Division of Biometrics 7 (DB7) reviewed these 5 studies.

The five studies are summarized in Table 1 and Table 2, below. All five studies were retrospective cohort studies using different databases including U.S. commercial claims, Veterans Affairs medical data (2 studies, 1 with linkage to external data sources), clinic and hospital medical records in the United Kingdom, and U.S. Medicare. The definition of a CV outcome also varied, from the use of a composite CV endpoint (All-cause mortality, myocardial infarction [MI] and stroke (Vigen)), non-fatal MI (Finkle), to evaluation of all-cause mortality (Shores, Muraleedharan), and hospitalization for MI (Baillargeon).

Two studies found statistically significant harm with TRT (Vigen and Finkle), two studies found statistically significant benefit with TRT (Shores and Muraleedharan) and one study found no change in risk (Baillargeon).

The Vigen study, conducted on male veterans post angiography with low testosterone levels from 2005 to 2011, found an increased risk with TRT compared to no TRT for a composite cardiovascular outcome (Hazard Ratio of 1.29 with 95% CI [1.04, 1.58]). The Finkle study, conducted on TRT users in a large claims database from 2006 to 2010, found an increased risk of non-fatal myocardial infarction during a post TRT period compared to the pre TRT period (Relative risk 1.36 with 95% CI [1.03, 1.81]). The Shores study, conducted in a population of male veterans older than 40 years of age with low testosterone from 2001 to 2005, found a decrease risk in all-cause mortality of TRT compared to no TRT (Hazard Ratio 0.61 with 95% CI [0.42, 0.88]). The Muraleedharan study was conducted in type 2 diabetic men in the United Kingdom from 2000 to 2005. The main analysis assessed mortality in men with low serum testosterone concentration compared to men with normal serum testosterone concentration. Mortality was assessed in a subsequent subgroup analysis of treated and untreated men with low serum testosterone concentration, and found an increased risk of all-cause mortality in men with no TRT compared to those on TRT (HR 2.30, 95% CI [1.30, 3.90]). Finally, the Baillargeon study, conducted in males older than 65 years enrolled in Medicare from 1997 to 2005, found that there was no overall increase in risk of hospitalization for MI when comparing those treated with TRT compared to those with no treatment (Hazard Ratio of 0.84 with 95% CI [0.69 - 1.02]). However, the investigators also obtained risk estimates stratified by a prognostic risk score for MI. Using this risk score, the investigators determined that men in the highest quartile of risk had a reduced risk of MI (HR of 0.69 with 95% CI [0.53-0.92]); this reduction of risk was not seen in the other 3 lower risk quartiles.

To increase the likelihood of identifying a symptomatic hypogonadal population, the Shores study used a lower threshold for low testosterone (<250 ng/dL) compared

to the Muraleedharan study (<300 ng/dL). In both studies, lower testosterone level was a predictor for TRT, but increased BMI and younger age were also predictors of TRT in the Shore study. The Baillargeon study did not use testosterone levels to select the cohort as no lab data were available from the claims data source, but indications for TRT (fatigue, hypogonadism, osteoporosis, sexual dysfunction) and increased comorbidity load (Elixhauser² score >3) were associated with TRT. In these three studies, these findings might indicate that testosterone was being used to treat men with lower baseline testosterone levels, or men with symptoms of hypogonadism, or both.

² A measurement of comorbidity using 30 conditions developed for use with large administrative data sets.

Table 1 – Summary of study designs

Design Features	Finkle et al., 2014	Vigen et al., 2013	Shores et al., 2012	Muraleedharan et al., 2013	Baillargeon et al., 2014
Objectives/ Aims/Scope	TRT and non-fatal MI in males	TRT and [all-cause mortality, MI and stroke] in males with low T ⁽¹⁾ who underwent angiography	TRT and Mortality, in male veterans with low T ⁽¹⁾	TRT and mortality in males with low T ⁽¹⁾ and type II diabetics	TRT and MI in older males
Exposure/ Intervention	Testosterone (gels, topicals, injections, micronized)	Testosterone (patch, gels, injections)	Testosterone	Testosterone (gels, buccal tablets, injections)	Intramuscular testosterone
Outcome(s)	Non-fatal MI (first event)	Composite: All-cause mortality, MI and stroke (first event)	Mortality	All-cause mortality	Hospitalization for MI (first event)
Comparisons of interest	(a) Self-control cohort: time pre TRT vs. time post TRT (b) TRT vs. PDE5-I	Users to non-users	Users to non-users	Users to non-users	Users of TRT to non-users (1:3)
Strengths	Large sample size Self-controlled cohort study can control for measured and unmeasured confounders	Large sample size Testosterone levels used to select the cohort	Testosterone levels used to select the cohort	Claims and medical records data Testosterone levels used to select the cohort	Large Sample Size Long follow up period Representation of all US geographic regions
Limitations	Testosterone levels not available in this database Reasons for initiating treatment unknown Short follow up time Possible prescribing bias in self-control cohort Lack of comparability of TRT to PDE5I in parallel cohort Unclear propensity weighting scheme in parallel cohort	Unknown cause of death Reasons for initiating treatment unknown Possible selection bias due to exclusion of events pre-TRT Possible misclassification bias of exposure Time on treatment not accounted for in ITT analysis	Excluded more recent data Small sample size Reasons for initiating treatment unknown Time on treatment not accounted for in ITT analysis	Excluded more recent data Small sample size Possible misclassification bias of exposure Time on treatment not accounted for in ITT analysis	Excluded more recent data Included only injections and not more recent formulations of TRT Could not include testosterone level (as baseline factor to define hypogonadism or risk factor for MI)
Abbreviations: TRT=Testosterone replacement therapy, MI=Myocardial infarction, Low T= Low testosterone, PDE5-I = phosphodiesterase 5 inhibitor, ITT=Intention to treat					

Table 2: Summary comparisons of study design features and results

Design Features	Finkle, 2014	Vigen, 2013	Shores, 2012	Muraleedharan, 2013	Baillargeon, 2014
Design Type	Retrospective self-control cohort (SCC) Retrospective cohort with parallel group (TRT & PDE5-I)	Retrospective cohort	Retrospective cohort	Retrospective cohort (TIMES2 trial follow-up)	Retrospective cohort
Data Source	Commercial claims database (MarketScan) in the US	VA clinical database in the US	VA clinical database, with linkage to outside death index data	Clinic and hospital medical records in the UK	5% national sample of Medicare in the US
Time Period	2006-2010	2005-2011	2001-2005	2000-2005	1997-2005
Study outcome	Non-fatal MI (first event)	Composite: All-cause mortality, MI and stroke (first event)	All-cause mortality	All-cause mortality deaths within 6 months of start to follow up excluded	Hospitalization for MI (first event)
Exposure cohorts/ Sample Size	⊕TRT: n=55,598 ⊕PDE5-I: n=167,279 (weighted 141,031)	⊕TRT: n=1,223 ⊘TRT: n=7,486	⊕TRT: n=398 ⊘TRT: n=633	⊕TRT: n=64 ⊘TRT: n=174	⊕TRT: n=6,455 ⊘TRT: n=19,065
Criterion (Selection) Standards	Males with ≥ 22 months continuous database enrollment and 90-days post treatment initiation	Male veterans post angiography, with low T (<300ng/dL)	Male veterans >40 years old with low T (<250ng/dL)	Type 2 diabetic males with low T (<300ng/dL) and at least 1 year of TRT	Males > 65 years enrolled in Medicare Part A and Part B for at least 12 months and no end-stage renal disease
Statistical Methods	Pre-TRT: 1 year; Post-TRT: 90 days SCC: Post/pre RR Parallel cohort: Propensity score weighting ATT(5) to estimate RR and weighted Poisson regression to estimate ratio of rate ratios (RRR)	Cox regression with stabilized inverse probability of treatment weights HR (95%CI); Weighted Kaplan Meier survival curves	Cox regression, with Time-varying TRT HR (95%CI); Unadjusted Kaplan Meier Curves; (Propensity score analysis [exploratory analysis])	Cox regression analysis HR (95%CI); Kaplan Meier Curves	Cohort selection: matching on author's developed MI prognostic score at baseline Analysis of outcome: Cox regression analysis HR (95% CI)
Follow up (FU) and Treatment Duration (TD)	FU: ≤ 90 days after 1st Rx	FU, Average: 27.5 months Average TRT TD: ~ 10-months	Average FU: 40 months Average TRT TD: 20-months	Average FU: 6 years Average TRT duration: 42-months (85% of cohort >24 months)	Average FU: ~ 3.5 years Median number of injections in study: 2.5
Primary Results Risk Estimate and (95% CI)	Post/Pre TRT, RR Overall: 1.36 (1.03, 1.81) <65 years: 1.17 (0.84, 1.63) ≥65 years: 2.19 (1.27, 3.77)	Intent to Treat 1.29 (1.04, 1.58)	Intent to Treat: HR 0.61 (0.42, 0.88)	Intent to Treat HR 0.43 (0.26, 0.77)	Intent to Treat: HR (0.84 (0.69 – 1.02)
Abbreviations: SCC=Self Control Cohort, VA = Veterans Affairs, UK=United Kingdom, MI=Myocardial infarction, TRT=Testosterone replacement therapy, Low T= Low testosterone, PDE5-I= Phosphodiesterase 5 inhibitor, FU= follow up, RR= Rate Ratio, HR=Hazard Ratio, MI=Myocardial Infarction, TD=Treatment duration					

Comments

Due to the differences in study design characteristics and methods of analysis, the results from these studies are difficult to integrate. The studies used different: databases, patient characteristics, formulations of testosterone, follow-up times, cardiovascular outcomes, and statistical methods to adjust for confounders or time varying covariates. Thus, none of the studies replicates the design of another study. It is unclear whether the differences in methodology, the differences in population characteristics, or a play of chance led to differences in findings.

Two major limitations with some or all of the five studies are noteworthy. The first is the lack of data on clinical decision making involved in prescribing TRT such as indications for TRT and disease severity. This made choosing an appropriate non-user comparator group for the TRT groups difficult and might have introduced confounding by indication. In pharmacoepidemiology, it is preferred to use a comparator group taking a drug or drugs treating the same disease as the drug of interest. However, there are no other drugs other than testosterone therapy approved to treat hypogonadism. In studies using a non-exposed comparator, the possibility of unmeasured confounding exists, despite having baseline characteristics data and utilizing complex statistical modeling. This highlights the need for investigators to consider alternative study designs and access to study populations with the relevant clinical data available.

The second limitation is the inability of these studies to separate the effect of TRT on CV risk from those of serum testosterone levels on CV risk. Testosterone levels over time affect both TRT dose prescribed and biomarkers associated with CV risk. In turn, TRT dose, adherence and effectiveness can affect testosterone levels over time. In order to examine both effects, a study would need the ability to measure serum testosterone concentrations at baseline and during the study period for both the exposed and unexposed patients.

DEPI and DB7 conclude that caution should be applied when interpreting the results of these five observational studies. All 5 studies are reasonably well conducted retrospective observational studies and the cardiovascular outcomes of MI, stroke, and mortality are endpoints with high positive predictive values in claims, medical records databases and death registries. Nevertheless, because of differences in study design, conduct, and analysis, it may not be advisable to integrate the studies' findings into a single summary statistic or estimate. However, the uncertainty around important factors leading to the use of TRT and the association of testosterone level with CV risk are difficult to assess without more detailed clinical data.

Conclusions

Drug utilization analysis demonstrates that testosterone use is increasing rapidly, and that the market is dominated by the topical products, followed by the injectable products. The majority of TRT users are men between the ages of 40-64 years, followed by those 65 to 74 years old. Concurrency analysis demonstrated that a majority of TRT therapy users also receive concomitant prescriptions for at least

one cardiovascular medication. DEPI's analysis of a commercially insured population indicated that the duration of use of TRT was generally short, with patients receiving a median of 3-months of treatment. The data also indicate that a small proportion of patients use therapy for longer periods, as the average duration of treatment was 6-months. For approximately 28% of the patients in our analysis, there was no evidence of serum testosterone concentration testing prior to the initial TRT prescription.

Based on the review of the meta-analysis of RCTs and the five observational studies, the evidence for increased risk of cardiovascular events with TRT is not conclusive. These observational studies do not provide convincing evidence for the benefit or risk associated with TRT due to the study limitations outlined; they do provide some information regarding the patient characteristics in the treated and untreated patient populations. These studies demonstrate that men who receive TRT are more likely to have underlying comorbidities. This observation is corroborated by DEPI's concurrency analysis which showed that over one-half of men prescribed TRT were receiving concurrent prescriptions for cardiovascular medication.

Additional studies, either clinical trial or epidemiological data, using data sources able to capture important baseline and time-varying characteristics including the diagnosis for TRT use, cardiovascular risk factors, and laboratory results are needed to better characterize the cardiovascular risks and benefits of TRT.

III. Memorandum - Office of Surveillance and Epidemiology, Division of Epidemiology II

b. Epidemiologist's Study Comparison Review

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Epidemiologist Study Comparison Review**

Date:	August 13, 2014
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Team Leader	CDR David Moeny, M.P.H, R.Ph., USPHS Division of Epidemiology II
Division Director	Judy Staffa, Ph.D., R.Ph. Division of Epidemiology II
Subject	DEPI-II qualitative review of meta-analysis of randomized controlled trials of testosterone therapy and placebo
Drug Name:	Testosterone

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LIST OF ABBREVIATIONS

CI	Confidence Interval
CRE	Cardiovascular-related Event
CV	Cardiovascular
DBRUP	Division of Bone, Reproductive and Urologic Drugs
DCRP	Division of Cardiovascular and Renal Products
DEPI	Division of Epidemiology
DPV	Division of Pharmacovigilance
DSC	Drug Safety Communication
FAERS	FDA Adverse Event Reporting Systems
FDA	Food and Drug Administration
IM	Intramuscular
MI	Myocardial Infarction
OR	Odds Ratio
ORP	Office of Regulatory Policy
PBO	Placebo
RCT	Randomized Controlled Trial
TSI	Tracked safety issue
TRT	Treatment
US	United States

EXECUTIVE SUMMARY

A variety of testosterone products are approved as replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary hypogonadism. In 2010, a Tracked Safety Issue (TSI)¹ was triggered after FDA was notified of the discontinuation of the Testosterone in Older Men with Mobility Limitations (TOM) trial due to a higher incidence of cardiovascular (CV)-related adverse events in the testosterone arm compared to placebo. After FDA reviewed this trial and other available data, the TSI was subsequently closed without issuance of a Drug Safety Communication or other regulatory action. The TSI was reopened in December 2013 following publication of the Vigen et al, 2013, study that suggested an increased risk of CV events in men receiving testosterone therapy. Subsequently, another large observational study and a meta-analysis of placebo-controlled trials have been published that also suggested a possible CV safety signal with testosterone therapy (Xu, Freeman, Cowling, & Schooling, 2013). In February 2014, a Citizen's Petition was submitted to FDA, citing these studies and requesting a boxed warning and other actions pertaining to CV risks associated with testosterone therapy. The Division of Epidemiology (DEPI) was asked to review the cited articles.

The purpose of this review is to provide a detailed epidemiologic assessment of the Xu meta-analysis with regard to evidence of CV harm with testosterone therapy and of the author's claim of a discrepancy between the results of the industry-funded and non-industry funded trials. For this review, DEPI evaluated the cited meta-analysis (Xu et al., 2013) and four accompanying additional files, as well as each of the individual component randomized controlled clinical trials (RCTs).

Combining the results of 27 published RCTs representing 2,994 men and 180 cardiovascular-related events (CREs), Xu et al. found that testosterone therapy was associated with an increased odds of a CRE (OR 1.5, 95% CI 1.1, 2.1; trim and fill OR 1.7, 95% CI 1.2, 2.4). When the analysis was restricted to serious CREs, the estimate was similar. The effect of testosterone therapy varied with source of funding (p-value for interaction 0.03). In non-industry funded trials, the odds ratio was greater (OR 2.1, 95% CI 1.3, 3.2) than in pharmaceutical industry-funded trials (OR 0.9, 95% CI 0.5 to 1.6).

Limitations of the study include inconsistent and incomplete reporting of adverse events, substantial clinical heterogeneity in the design and conduct of the component trials, as well as in the types of cardiovascular outcomes reported, potential bias resulting from

¹ A Tracked Safety Issue (TSI) refers to the tracking of activities implemented when FDA investigates significant safety issues associated with marketed drugs that require input from several FDA Divisions, Offices, another FDA Center, and/or that require a regulatory briefing, Drug Safety Oversight Board meeting, or advisory committee meeting) for their evaluation.

selection of component trials, and variable quality of the trials, particularly with regard to ascertainment of cardiovascular safety outcomes. The noted discrepancy in CRE risk estimate based on funding source (non-industry versus industry funded), while interesting, was based on a post-hoc analysis. The observed difference may have been due to chance or to differences in study design or adverse event reporting. Although the Xu meta-analysis was carefully conducted and the paper well-written, DEPI concludes that, because of substantial methodological limitations, this study does not provide convincing evidence of a causal association between testosterone therapy and adverse cardiovascular events.

1 INTRODUCTION

1.1 BACKGROUND AND REGULATORY HISTORY

Testosterone is an androgen steroid hormone, secreted primarily by the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In males, testosterone is key in the development of male reproductive tissues and promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair.

Testosterone products have been approved in the U.S. since the 1950s to stimulate puberty, and for the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in males. Some formulations have also been approved for the treatment of metastatic mammary cancer in women. Testosterone products are approved as replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism. Currently approved formulations include a topical gel, transdermal patch, intranasal gel, buccal system (applied to upper gum or inner cheek), and injection.

In 2010, a Tracked Safety Issue (TSI) was opened after a premature discontinuation of the TOM trial due to a higher incidence of cardiovascular (CV)-related adverse events in the testosterone gel arm compared to placebo. FDA's Division of Cardiovascular and Renal Products (DCRP) reviewed the study and concluded that the results were inconclusive due to the lack of a prespecified safety endpoint, potential ascertainment bias, the small number of major adverse cardiac events reported, possible imbalances in baseline cardiovascular risk between the groups, and questionable applicability to the population for whom testosterone therapy is indicated. After a thorough review that included other available data (two meta-analyses and a systematic review) under the TSI, the Division of Epidemiology (DEPI) also concluded that the data do not support an association between testosterone therapy and an increased risk of cardiovascular events in men. Both DCRP and DEPI concluded, however, that the evidence fell short of providing a definitive answer to the question of testosterone and cardiovascular risk. The TSI was closed without issuance of a Drug Safety Communication (DSC) or other regulatory actions.

The TSI was reopened in December 2013 following publication of the Vigen et al, 2013, study, suggesting an increased risk of cardiovascular events in men prescribed testosterone therapy. A publication of another large observational study (Finkle et al, 2014) followed, which also suggested the same safety signal. FDA issued a DSC in January 2014 announcing that it is reassessing the cardiovascular safety of testosterone

therapy and is “investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.”²

1.2 LABELING

Current testosterone product labeling contains the following warnings and precautions broadly related to the cardiac and vascular systems (none are boxed warnings):

- **Edema:** Edema, with or without congestive heart failure (CHF), may be a complication in patients with preexisting cardiac, renal, or hepatic disease.
- **Lipids:** Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy.
- **Polycythemia:** Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of testosterone.... An increase in red blood cell mass may increase the risk of thromboembolic events.
- **Venous thromboembolism (VTE):** Venous thromboembolism, including deep vein thrombosis (DVT) and acute pulmonary embolism (PE), have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT and PE.³
- **Sleep apnea:** The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung disease.

The testosterone cypionate injection label contains a contraindication for ‘patients with serious cardiac, hepatic, or renal disease.’ The testosterone enanthate injection label states “because androgens may alter serum cholesterol concentration, caution should be used when administering these drugs to patients with a history of myocardial infarction or coronary artery disease.” These testosterone injectable products were approved several decades ago, when standards and practices governing labeling differed from those of testosterone products approved more recently.

² FDA Drug Safety Communication: FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. January 31, 2014.
<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM383909.pdf>

³There is currently a separate TSI in process to harmonize the labels with regard to VTE risk.
<http://www.fda.gov/drugs/drugsafety/ucm401746.htm>

1.3 SAFETY QUESTIONS FOR DEPI REVIEW

In February 2014, a Citizen’s Petition was submitted to FDA regarding the evidence presented in the two recent observational studies (Vigen et al., 2013; Finkle et al., 2014), as well as a recent meta-analysis of placebo controlled RCT’s (Xu et al., 2013). The petitioner requested a boxed warning for testosterone products based on the evidence presented in the cited studies, among others.

The purpose of this review is to provide a detailed epidemiologic assessment of the cited Xu meta-analysis.

2 METHODS AND MATERIALS

For this review, DEPI evaluated the cited Xu et al. meta-analysis and the four supplemental online files accompanying this publication: Additional File 1. PRISMA 2009 checklist; Additional File 2. Trials where authors contacted for additional information and responses; Additional File 3. Quality assessment of the selected placebo-controlled RCTs of the effects of testosterone therapy on CREs; and Additional File 4. Description of CREs in the selected placebo-controlled RCTs (Xu et al., 2013). Additional Files 2-4 are included in Appendices B-D. Each of the component RCTs included in the meta-analysis was also reviewed individually, as summarized in Appendix A. This review includes a summary of the study methods and results, a description of the component RCTs, discussion of methodological considerations, study strengths and limitations, and an overall evaluation of the evidence provided regarding testosterone and cardiovascular harm. The 2011 publication by FDA epidemiologists “Secondary use of randomized controlled trials to evaluate drug safety: a review of methodological considerations” (Hammad, Pinheiro, & Neyarapally, 2011) provided guidance for this review.

3 RESULTS

3.1 STUDY OVERVIEW

Table 1 – Xu Meta-analysis Study Overview

	Study
1.1 Objectives/Aims/Scope	To examine the overall risk of cardiovascular-related events (CREs) associated with testosterone therapy
1.2.1 Design	
1.2.1.1 Type	Systematic review and meta-analysis of published RCTs

1.2.1.2 Data Source	PubMed and WHO International Clinical Trials Registry Platform, with additional information sought from study authors
1.2.1.3 Time Period and setting	Studies published through December 31, 2012, both within and outside the U.S.
1.2.1.4 Criterion (Selection) Standards	RCTs of testosterone therapy in men, of at least 12 weeks duration, that report cardiovascular (CV) events by study arm
1.2.2 Exposure/Intervention	Testosterone (but not other androgens) in any dose, formulation, or route of administration
1.2.3 Outcome(s)	<u>Primary</u> : Composite cardiovascular-related events (CREs), as reported by component study authors <u>Secondary</u> : Serious cardiovascular events, cardiovascular death
1.2.4. Covariates	Funding source, baseline testosterone
1.2.5 Sample Size	27 studies: 1,733 in testosterone arms, 1,261 in placebo arms
1.2.6 Statistical Analyses	I^2 to assess heterogeneity Fixed and random effects models Pooled odds ratio using inverse variance weighting Meta-analysis regression Funnel plot and 'trim and fill'
1.2.7 Study Results	Testosterone therapy (TRT) increased the odds of a CRE (OR 1.54 [95% CI 1.09, 2.18]). Trim and fill revised the OR to 1.69 (95% CI 1.21, 2.38). When analysis restricted to serious CREs, estimate was very similar (OR 1.61 [95% CI 1.01, 2.56]), revised to 2.01 (95% CI 1.30, 3.14) by trim and fill. Effect of testosterone therapy varied with source of funding (p-value for interaction 0.03), but not with baseline testosterone level (p-value for interaction 0.70). In non-industry funded trials, odds ratio was greater (OR 2.06 [95% CI 1.34, 3.17]) than in pharmaceutical industry funded trials (OR 0.89, 95% CI 0.50 to 1.60).

3.2 STUDY DESIGN

3.2.1 Study Type

This study was a systematic review and meta-analysis of RCTs, following a published protocol. The investigators state that they followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

3.2.2 Data Sources and Time Period

Two study investigators independently searched PubMed for publications up to December 31, 2012, using the search terms “(“testosterone” or “androgen”) and (random*) and trial”, limited to male gender and studies in English. The reviewers also searched the World Health Organization International Clinical Trials Registry for trials using testosterone as an intervention. Trials deemed irrelevant based on title or abstract were excluded. Bibliographies of the selected trials and relevant reviews were also searched for potential RCTs. The investigators also sought clarification concerning events by study arm for 10 trials; however, only one of these queries yielded useful information.

3.2.3 Criterion (Selection) Standards

Only placebo-controlled RCTs that reported cardiovascular-related events (CREs) by study arm were selected, including trials that only reported adverse events leading to withdrawals. Studies that were not RCTs and trials reporting treatment-related events only in the testosterone arm, and not in the control arm, were excluded. RCTs less than twelve weeks treatment duration were excluded “to assess long-term rather than acute effects of testosterone therapy,” and duplicate studies using the same trial participants were excluded. The analysis included any RCT of testosterone, but not other androgens, compared with placebo, including comparisons against a background of treatments for other conditions.

According to the Xu article, 138 out of 169 potentially relevant articles were excluded for the reasons noted above. The authors informed DEPI that 35 studies were excluded because they did not report CV-related events by trial arm; 51 because the intervention was less than 12 weeks; 31 because they were not RCTs or had no control group; and 21 because they were duplicates.

3.3 EXPOSURE/INTERVENTION

The intervention was defined as testosterone therapy. Formulation, dose, and duration of therapy were documented.

3.4 OUTCOME

The primary outcome was a composite of CREs, defined as anything reported by the authors of the component studies as cardiac disorders, CV complaints, CV events, vascular disorders, cardiac or cardiovascular, or where the event description fell within the ICD-10 codes I00 to I99: Diseases of the circulatory system. Serious cardiovascular events were defined as those which the component study authors described as serious adverse events or where the outcome was death, life-threatening, hospitalization, involved permanent damage or required medical or surgical intervention, or was one of the following types of cardiovascular events: myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke or congestive heart failure but not deep vein thrombosis (see Appendix D).

3.5 COVARIATES

In the meta-analysis regression, baseline testosterone level and funding source were included as covariates to assess whether the effects of testosterone varied by these factors.

3.6 SAMPLE SIZE

Final sample size included 27 trials with 2,994 mostly middle-aged or older male participants (1,733 testosterone and 1,261 placebo). A total of 180 CREs were reported among these participants.

3.7 STATISTICAL ANALYSIS

The total number of participants randomized was used as the denominator and all CREs were included in the analysis. Funnel plots and ‘trim and fill’ were used to assess publication bias. I^2 was used to assess heterogeneity between trials, using fixed effects models where heterogeneity was low ($I^2 < 30\%$), otherwise using random effects models. The pooled odds ratio was estimated using the ‘metabin’ function of the ‘meta’ package in R version 2.14.1, and meta-analysis regression, with inverse variance weighting, was used to assess whether the effects of testosterone therapy varied with baseline testosterone and funding source, using the ‘rma’ function of the ‘metafor’.

3.8 META-ANALYSIS STUDY RESULTS

From an initial 1,882 citations identified, 169 potentially relevant articles were examined, and three additional articles were identified from previous meta-analyses and the WHO registry. Twenty-seven articles were selected for inclusion in the systematic review and meta-analysis. A total of 115 CREs (in 1733 participants) occurred in the testosterone treatment (TRT) groups, and 65 in the placebo groups (in 1261 participants).

The I^2 analysis demonstrated overall homogeneity in the trial results ($I^2 = 7.8\%$), as shown in the forest plot (Figure 1). Using a fixed effect model, TRT was associated with an increased odds of a CRE (OR 1.5, 95% CI [1.1, 2.1]) relative to placebo.

Figure 1: Forest plots of placebo-controlled randomized trials examining the pooled effect of testosterone therapy on cardiovascular-related events.

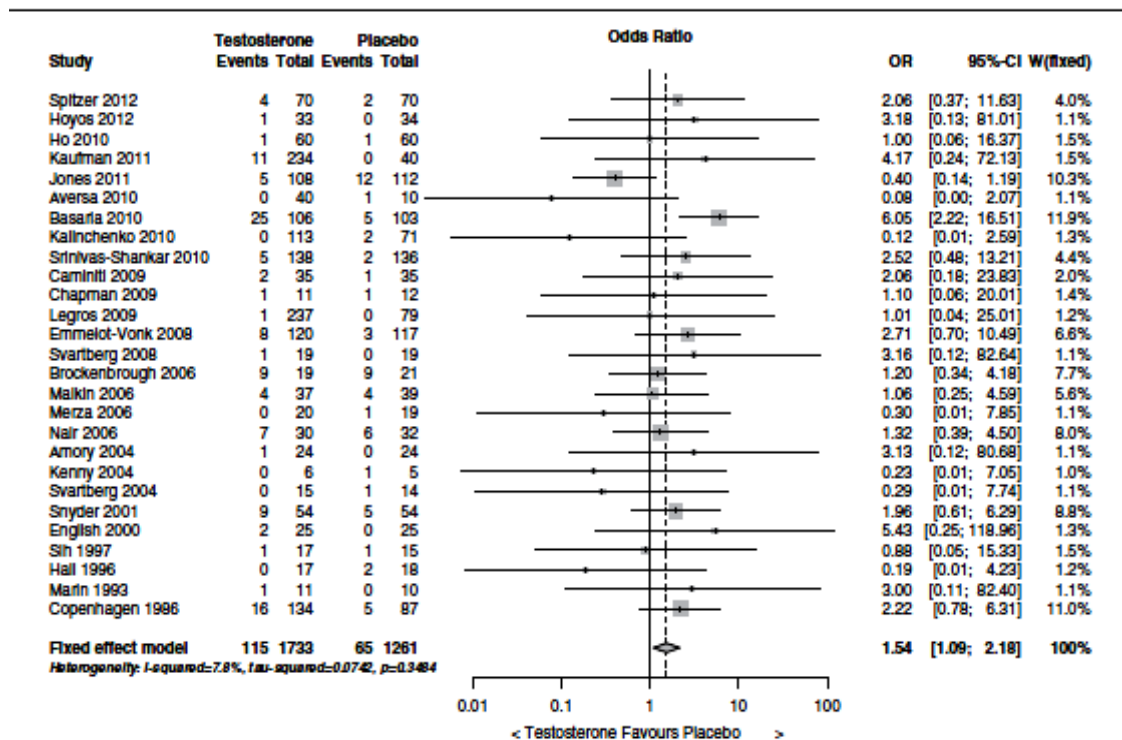


Figure 1 in Xu et al., 2013.

A funnel plot was used to assess for the possibility of publication bias, plotting the distribution of component study odds ratios against their standard errors (inversely related to study size) around a line indicating the summary odds ratio (Figure 2). The funnel plot suggested some asymmetry, with several small studies to the far left of the pooled odds ratio line (TRT associated with a lower risk of CREs) but no similar small studies to the far right (TRT associated with a higher risk of CREs). The pooled OR was recalculated using a trim and fill method to account for these potentially missing studies, and the point estimate shifted slightly further away from the null (OR 1.7 [95% CI 1.2, 2.4]).

When the analysis was restricted to serious CREs, the estimate was similar (OR 1.6 [95% CI 1.0, 2.6]) and increased to 2.0 (95% CI 1.3, 3.1) with trim and fill. Thirty-three CV-related deaths were identified (22 testosterone, 11 placebo), with a non-significant OR of 1.4 (95% CI 0.7, 2.9), revised to 1.6 (95% CI 0.8, 3.1) by trim and fill.

Figure 2: Funnel plot of placebo controlled randomized trials examining the effects of testosterone therapy on cardiovascular-related events.

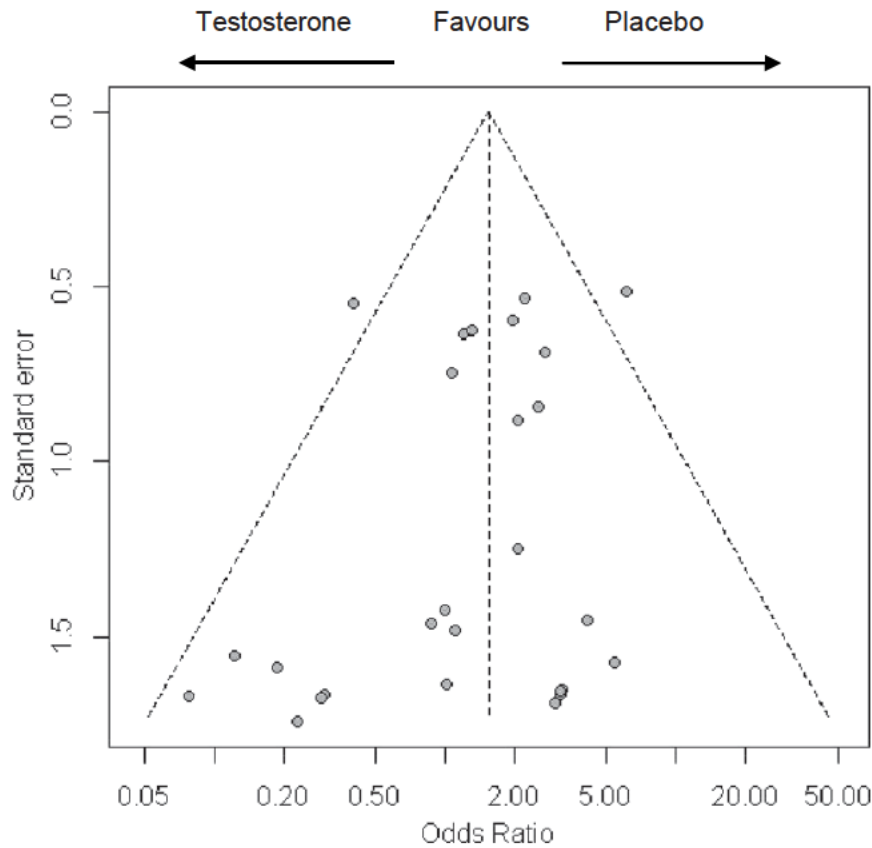


Figure 2 in Xu et al., 2013.

The investigators also conducted a *post hoc* analysis to assess whether the CRE rate was lower in trials funded by the pharmaceutical industry than in non-industry funded trials. The results of this analysis showed that in the 13 studies funded by the pharmaceutical industry, TRT had no effect on CREs (OR 0.9 [95% CI 0.5, 1.6]), but in the other 14 trials TRT substantially increased the odds of a CRE (OR 2.1 [95%CI 1.3, 3.2]) (Figure 3). The odds of CREs on TRT varied significantly with the source of funding (p-value for interaction 0.03), but did not vary with baseline testosterone level (p-value for interaction 0.7).

Figure 3: Forest plots of placebo-controlled randomized trials examining the pooled effects of testosterone therapy on cardiovascular-related events by source of funding (upper panel contains studies funded by the pharmaceutical industry, and lower panel contains studies not funded by the pharmaceutical industry)

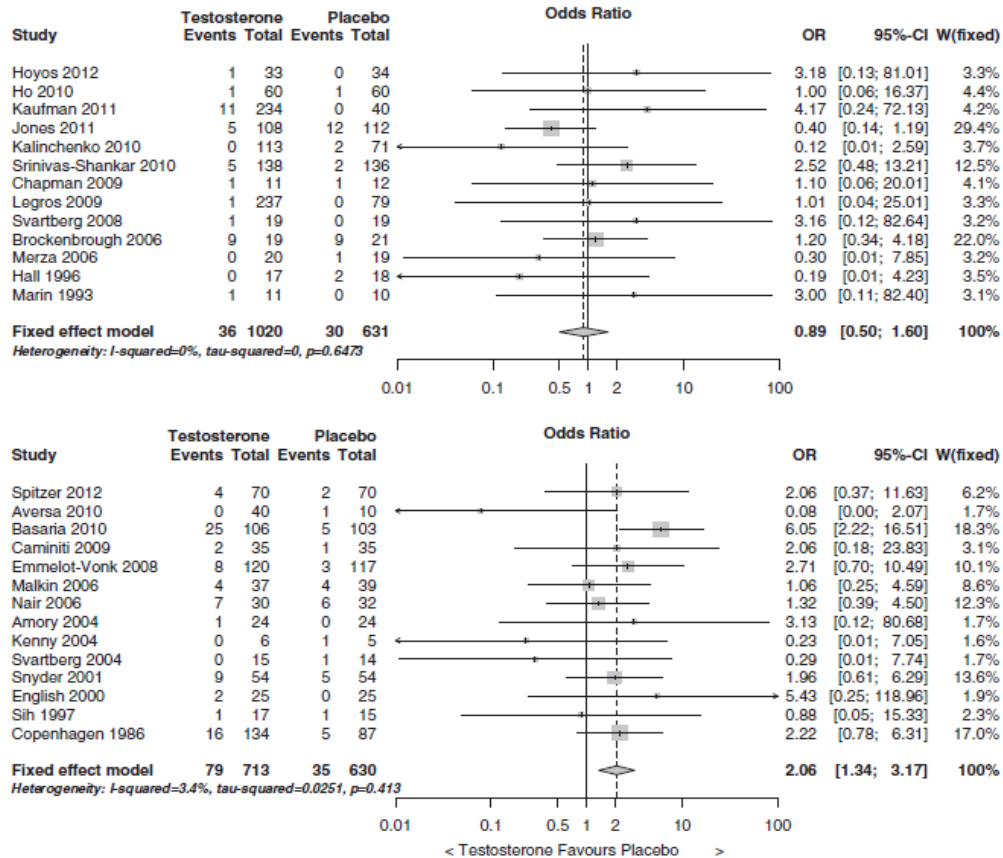


Figure 3 in Xu et al., 2013.

3.9 REVIEW OF COMPONENT STUDIES INCLUDED IN THE META-ANALYSIS

Descriptions of the individual component studies are provided in **Appendix A** (Amory et al., 2004; Aversa et al., 2010; Basaria et al., 2010; Brockenbrough et al., 2006; Caminiti et al., 2009; Chapman et al., 2009; 1986; Emmelot-Vonk et al., 2008; English, Steeds, Jones, Diver, & Channer, 2000; Hall, Larbre, Spector, Perry, & Da Silva, 1996; Ho et al., 2012; Hoyos et al., 2012; Jones et al., 2011; Kalinchenko et al., 2010; Kaufman et al., 2011; Kenny, Fabregas, Song, Biskup, & Bellantonio, 2004; Legros et al., 2009; Malkin et al., 2006; Marin et al., 1993; Merza et al., 2006; Nair et al., 2006; Sih et al., 1997; Snyder et al., 2001; Spitzer et al., 2012; Srinivas-Shankar et al., 2010; Svartberg, Aasebo, Hjalmsen, Sundsfjord, & Jorde, 2004; Svartberg et al., 2008).

3.9.1 Study Design

All the component studies were RCTs of testosterone therapy (TRT) of at least 12 weeks in duration. The interventions ranged, however, from 12 weeks to 3 years of treatment. Sample sizes were generally small, with nearly one-half (12/27 or 44%) of the studies including 50 or fewer participants. The primary study objectives varied widely, examining the effect of testosterone on efficacy outcomes such as bone mineral density, body composition, angina threshold, serum lipid profile, insulin resistance, pulmonary function, cognitive function, functional capacity, aerobic exercise capacity, quality of life, and erectile dysfunction.

3.9.2 Study Setting, Population, and Inclusion/Exclusion Criteria

Of the 27 component studies, ten were conducted in the U.S. The study populations, and inclusion and exclusion criteria varied widely, particularly with respect to age, comorbidities, baseline cardiovascular risk, and baseline testosterone levels. Some studies were limited to older men (Amory, Basaria, Caminiti, Chapman, Emmelot-Vonk, Kenny, Nair, Srinivas-Shankar, Svartberg 2008) while others also included young to middle-aged men, and a few excluded older men, (Aversa, Ho, Spitzer, Kalinchenko). Some studies attempted to recruit a generally healthy population, excluding significant medical illnesses (Amory, Ho, Hoyos, Kaufman, Marin, Merza, Nair, Sih, Svartberg 2008), while other studies had samples enriched for serious comorbidities, CV risk factors, or pre-existing CV disease (Aversa, Basaria, Brockenbourg, Caminiti, Copenhagen study, Emmelot-Vonk, English, Hall, Jones, Kalinchenko, Malkin, Spitzer, Srinivas-Shankar, Svartberg 2004). Inclusion criteria also varied with regard to baseline androgen status. In some studies, hypogonadism was not part of the inclusion criteria (Caminiti, Chapman, Copenhagen, English, Hall, Hoyos, Malkin, Svartberg 2004), while other studies included only men with documented hypoandrogenism, although laboratory measurement and definitions varied in these studies as well.

3.9.3 Intervention

The interventions differed substantially across studies. There was virtually no consistency across studies in dose/frequency, duration, formulation, and route of administration for testosterone therapy. A few studies titrated dose to target serum testosterone levels, while others used a fixed dose, and others decreased doses at pre-specified intervals in cases of elevated hematocrit or PSA. (See Appendix A)

3.9.4 Ascertainment and reporting of CV Events

Additional file 4 (Xu et al. 2013), included as Appendix D, as well as DEPI's review of the individual RCTs (Appendix A) describe the CREs included in the analysis. Although Xu et al. did not conduct an analysis employing the commonly used composite outcome Major Adverse Cardiac Events (MACE), based on the descriptions of the events, FDA

enumerated a subset of the reported CREs that appears to be consistent with MACE. Using the narrow definition of MACE, which consists of myocardial infarction, ischemic stroke, and CV death, the event rate would be 1% in both the TRT and PBO groups (18/1733 vs. 12/1261, respectively). Using the broad definition of MACE, which consists of myocardial infarction, stroke, and all-cause mortality, the event rate would be 1.8% in the TRT group and 1.4% in the PBO group (32/1733 and 18/1261 respectively), with all the additional deaths in the TRT group arising from bleeding esophageal varices with the exception of one death from constrictive pericarditis. The remaining CREs either clearly would not be considered MACE or contained too little detail to determine whether the events were MACE. These included such events as venous thrombosis, hypertension, arrhythmias, phlebitis, worsening heart failure, edema, syncope, chest pain, tachycardia, carotid bruit, “cardiovascular complaints,” and “other vascular events.”

Two studies pre-specified CV safety events (Basaria, Emmelot-Vonk), and seven described blinding of the individuals assessing outcomes, including adverse events (Basaria, Copenhagen study, Emmelot-Vonk, Hoyos, Jones, Spitzer, Srinivas-Shankar). (Also see Appendix C, Xu Additional File 3. Of note, DEPI’s determination of studies’ pre-specification and outcome assessor blinding, included in Appendix A, differed slightly from Xu et al.’s. Two studies (Basaria, Snyder) reported verification of adverse events through medical record review. Some studies (Ho, Kalinchenko, Merza, Hall, Marin, Sih) appeared to report only CREs resulting in study withdrawal, while others reported CREs more broadly.

3.9.5 Study Retention

Most studies had retention rates of at least 80%, although a number had discontinuation rates of greater than 20% overall or in at least one study arm (Amory, Brockenborough, Chapman, Hoyos, Jones, Kaufman, Legros, Malkin, Nair). Additional studies either described differences in retention by study arm or did not report discontinuation rates by study arm (Amory, Chapman, Jones, Srinivas-Shankar, Snyder, Svartberg 2004). Two studies were stopped early, one due to cardiovascular safety concerns (Basaria—TOM trial), and one following a provisional comparison showing that it would not be feasible to demonstrate a survival benefit of testosterone in the foreseeable future (Copenhagen study).

3.9.6 Funding Source

As noted by Xu et al., the authors of 13 studies reported receiving direct industry funding. Of the remaining 14 studies categorized by Xu et al. as non-industry funded, five reported using medication provided by pharmaceutical companies and eight either did not provide clear information on funding source or described industry consultancies or other industry ties. Industry-funded studies tended to include participants who were, on average, younger and with fewer comorbidities and lower CV risk than the remaining studies

(based on information provided in the published component studies, which was often incomplete).

4 DISCUSSION

The Xu meta-analysis does not, by itself, provide convincing evidence of a causal association between testosterone therapy and adverse cardiovascular events. The paper was well-written and followed a published protocol and recommended guidelines for reporting of meta-analyses (PRISMA). The additional files provided details that were useful in interpreting the study results. Substantial methodological issues limit the conclusions that can be drawn from these results, however. Major issues for this meta-analysis include the well-known problem of incomplete safety data reporting in published clinical trials, the clinical heterogeneity of the component trials and endpoints, and the unknown impact of trial selection, particularly the exclusion of shorter trials. A number of methodological limitations in the individual component trials also decrease the strength of the overall findings. The discrepancy that Xu et al. identified in testosterone-associated risk between industry-funded and non-industry funded trials could reflect differential adverse event reporting, although this was not a pre-specified analysis and may have been the result of chance. Other differences in the design and conduct of the trials may also have contributed to the observed association between funding source and risk estimates.

Methodological considerations:

- *Incomplete adverse event reporting in published trials:* Incomplete reporting of adverse events in both the component RCTs, as well as in excluded studies, is a major concern in the interpretation of the Xu study. Wide variation in adverse event reporting in published trials in general has been well-documented, and in a substantial proportion of published trials, information on adverse events is not included at all (Ioannidis, 2009). Xu et al.'s exclusion of studies reporting CREs only in the TRT arm was appropriate and conservative; however, the need to exclude more trials for lack of adequate reporting (35 trials) than were included in the meta-analysis (27 trials) creates considerable uncertainty about the meta-analysis results due to the large amount of missing data. The asymmetry in the funnel plot suggests that these data may not be missing at random, but given the large number of excluded studies, the funnel plot and trim and fill analyses cannot sufficiently account for the missing safety data. Additional File 2 (Xu et al., 2013), included as Appendix C, describes in detail nine trials that were either excluded entirely or only a subset of cardiovascular outcomes included because of incomplete or conflicting information. Inclusion of just these trials could potentially add almost 40 additional CREs to the analysis, a number that could substantially affect a summary estimate based on 180 events. Based on the authors' description of the unconfirmed (and excluded) events, it

appears that including them would likely have strengthened the findings of the meta-analysis (shifted results further away from the null), but this cannot be established due to incomplete information available to DEPI. Among six included trials reporting only withdrawals, it is also unknown whether other CREs—including types of events reported in other trials and included in the meta-analysis—may also have occurred. While the generally conservative selection of trials and the funnel plot results help to support the conclusions of the meta-analysis, the overall problem of incomplete safety data reporting remains a fundamental weakness of this type of meta-analysis using published data.

- *Clinical heterogeneity:* Although the component trials were found to be homogeneous and suitable for integration from a statistical standpoint, a major question is whether the component trials in the Xu meta-analysis are suitable for integration from a study design and clinical perspective. Because findings of the individual RCTs have widely varying overall risk estimates and the trials suggest both CV benefit and harm, potential reasons for these differences must be considered, including the possibility of true differences in drug effect under various conditions and in different populations as well as conflicting results due to differences in measurement and reporting of data. The component RCTs included in this meta-analysis were also heterogeneous in almost all aspects of study design—age of participants, inclusion and exclusion criteria, study duration, drug formulation and dose—as well as in the manner in which safety events were ascertained. The reported incidence of CREs in the component trials ranged from <1% (Legros) to 45% (Brockenbrough), likely reflecting the substantial heterogeneity both in trial design factors, such as trial duration and baseline cardiovascular risk, and in adverse event reporting. The latter is of particular concern given the inconsistency in RCT safety data reporting.

Xu et al. defined the primary outcome as “composite cardiovascular-related events” because they anticipated too few events for a robust assessment by CRE type. Just as in clinical trials, however, one must determine whether a composite outcome is appropriate. Unlike the commonly-used MACE composite outcomes (stroke, MI, and either CV death or all-cause mortality), the composite outcome used in this meta-analysis gives equal weight to events ranging from “peripheral edema” to “other vascular events” to “death from myocardial infarction” (see Appendix D). While combining these clinically heterogeneous events with widely varying severity and biological mechanisms may provide the necessary power to detect a difference between treatment arms, the aggregated outcome is difficult to interpret and may mask or distort the signal for the most clinically important CV outcomes. The similar results found in a secondary analysis restricted to serious events strengthens the study’s findings somewhat, as reporting of these events may be more consistent.

However, even this subset was quite heterogeneous clinically, including such events as “death from bleeding esophageal varices,” “constrictive pericarditis,” and “early elective coronary angioplasty,” while excluding “cardiac disorders not involving death.” Although beyond the scope of this review, it is also not clear whether all of the outcomes included can plausibly be attributed to testosterone. Looking just at MACE outcomes (although generally without prespecification, consistent blinding, or adjudication of events), the imbalance between TRT and placebo groups is minimal, although DEPI did not conduct a formal statistical analysis using MACE outcomes.

- *Selection of trials:* The use of two independent investigators to search for and select trials and the removal of duplicate trials were strengths of this meta-analysis. Because of the need to select trials based on an examination of the outcome of interest, however, unintended bias on the part of the investigators cannot be entirely ruled out. Also, the appropriateness of excluding shorter trials is questionable, particularly given the large number of shorter-duration trials (51 trials) that were excluded for this reason. Because of the complex interplay of multiple biological pathways in the relationship between testosterone and CV risk, CV effects of testosterone may vary across treatment time. Both risks and benefits arising early in testosterone therapy are biologically plausible, and epidemiologic studies have suggested risks early in therapy (Finkle et al., 2014). Moreover, shorter trials may be less vulnerable to biases that can arise from differential study discontinuation and loss to follow up. It is possible that the systematic exclusion of a subset of adverse events occurring early in treatment could create bias of unpredictable magnitude and direction.
- *Within-study limitations and considerations:* A number of methodological issues also pertain to the design and conduct of the individual component trials.
 - Sample size and randomization: While all included trials were RCTs, substantial portions were pilot studies or trials with very small sample sizes (and very low event rates), and a number of trials had study arm imbalances in cardiovascular risk factors and pre-existing cardiovascular disease (Basaria, English, Ho, Kenny). Many of the trials lacked information on relevant baseline parameters and cardiovascular risk factors, and it was therefore often not possible to determine whether there was an imbalance in these risk factors, particularly in the smaller trials.
 - Safety outcome ascertainment: Only seven trials reported that the monitoring clinician or safety assessor was blinded to study drug, and only two used clearly pre-specified CV safety outcomes, and only two reported verification of adverse events through medical record review. Therefore, in general, the component trials were not designed to assess CV risk with TRT and lacked important features such

as prespecified adjudication of events. The general lack of blinded assessment and use of pre-specified CREs may increase the risk of ascertainment bias in the component trials. Furthermore, exogenous testosterone can produce noticeable changes in body habitus, potentially unmasking participants and clinicians to study drug and creating bias with respect to patient reporting or clinician assessment of adverse events.

- Discontinuation: Trials varied widely in their discontinuation rates, but roughly a third of trials had discontinuation rates that were high enough to potentially undermine the benefits of randomization with respect to the balance of both known and unknown confounders. Others did not report discontinuation rates by trial arm or reported differences by trial arm, raising the possibility of informative censoring. Where reasons for discontinuation were reported, many were due to elevated prostate-specific antigen (PSA) or hematocrit, events more likely to occur in the testosterone replacement therapy (TRT) arm. While these TRT group discontinuations would be expected to bias safety results toward the null by limiting the opportunity for development of adverse events in the TRT arm, thus strengthening the meta-analysis conclusions, this pattern was not consistent across trials.

Subgroup analysis based on funding source:

Xu et al.'s analysis of CRE risk based on funding source, while interesting, was not a pre-specified analysis and the results may have been due to chance. Moreover, some of the trials that were classified as non-industry-funded actually did not clearly state their source of funding or lack of industry ties. The observed difference in effect could result from a combination of factors, including differences in adverse event reporting, trial duration, baseline cardiac risk of study participants, discontinuation rates, or drug formulation or dose. A number of differences are apparent between industry funded and non-industry funded trials, as grouped by Xu et al. First, trial duration was, on average, longer for non-industry funded trials. Industry-funded trials also included participants who were, on average, younger and had a lower prevalence of pre-existing cardiovascular disease and cardiovascular risk factors (based on information provided in the published component studies, which was not always complete). While these differences in age or baseline CV risk should affect the incidence of cardiovascular-related events in both the treatment and placebo arms, these factors could modify the risk associated with testosterone treatment. There was also some suggestion of differential reporting of adverse events, with 5 of 13 industry-funded trials and only one other trial reporting only events that resulted in trial withdrawal.

5 CONCLUSIONS

Although the Xu meta-analysis was carefully conducted and the paper well-written, DEPI concludes that, because of substantial methodological limitations, this study does not provide convincing evidence of a causal association between testosterone therapy and cardiovascular events. Limitations of the study include the inconsistent and incomplete reporting of adverse events, substantial clinical heterogeneity in the design and conduct of the trials as well as in the types of cardiovascular outcomes reported, potential bias resulting from selection of component trials, and variable quality of the trials, particularly with regard to ascertainment of cardiovascular safety outcomes. The noted discrepancy in CRE risk based on funding source, while interesting, was not a pre-specified analysis and may have been due to chance or to differences in study design or adverse event reporting.

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7 APPENDICES

7.1 APPENDIX A: DEPI SUMMARY TABLE OF COMPONENT RCTs

Key: AE=adverse event; BPH=benign prostatic hypertrophy; CA=cancer; CABG=coronary artery bypass graft; CHF=congestive heart failure; CVA=cerebrovascular accident; ESRD=End stage renal disease ; HCT=hematocrit; HGB=hemoglobin; HTN=hypertension; LTFU=loss to follow-up; MI=myocardial infarction; NYHA=New York Heart Association; NR=not reported; NS=non-significant; PBO=placebo; PSA=prostate-specific antigen; PVD=peripheral vascular disease; T=testosterone; TRT=treatment

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Amory, 2004 2. U.S. 3. Not stated	1. 36 months 2. T enanthate 200mg IM every 2wks (Potential for dose-reduction of T for hct>52%)	1. TRT n=24; PBO n=24 2. IC: 65+ years and total T <12.1 nmol/l 3. EC: severe illness, use of anabolic steroids, antiandrogens, glucocorticoids, bisphosphonates, diuretics, calcitonin, seizure meds, warfarin; Paget's disease; smoking or heavy alcohol use, sleep apnea, hematocrit>48%; total cholesterol>300mg/dl; abnormal kidney, liver, thyroid, adrenal, or pituitary function; regular exercise >3x/week; prostate CA/nodule or PSA>4.0 or Prostate Symptoms Score>8; elevated urinary post-void residual, abnormal transrectal ultrasound 4. Mean age 71 (range 65-83)	Any serious adverse CV, cerebrovascular, or pulmonary events 1. No 2. NR	1 cerebral hemorrhage in testosterone-only arm	1. Relatively low CV risk except older age. Important CV risk factors excluded: smoking, use of diuretics (would exclude many w/ HTN), total chol>300 2. BMI (27-28), age (71) balanced, but most CV risk factors unknown 3. 29% discontinuation rate, study arm not specified. Telephone f/u conducted for men who discontinued prematurely	Older, but generally healthy population. <u>Strengths:</u> 1. Long trial duration <u>Limitations:</u> 1. 29% discontinuation rate. Only 2 lost to follow-up, but unclear whether non-prostate outcomes were assessed in follow-up calls. Arm-specific number of drop-outs not specified 2. CV/safety outcomes not prespecified; unclear if blinded

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Aversa, 2010 2. Italy 3. Not stated	1. 12-months (with 12 month open-label extension) 2. T undecanoate (TU) 1000mg q 12 weeks	1. TRT n=40; PBO n=10 2. IC: 45-65 years old with metabolic syndrome and/or Type 2 diabetes AND total serum T level <3.0 ng/ml or calculated free T levels <250 pmol/L AND ≥ 2 symptoms of hypogonadism 3. EC: Androgen therapy or anabolic steroid use; history of prostate or breast CA; drug or alcohol abuse; history of tumors, blood coagulation irregularities; symptomatic obstructive sleep apnea; HCT≥52%; elevated PSA or abnormal digital rectal exam; use of 5-alpha-reductase inhibitors; uncontrolled endocrine disorder including HbA1c ≥ 9; NYHA class III or IV heart failure; hepatic or renal insufficiency; severe neurological and psychiatric disease; requiring or undergoing fertility treatment. 4. Mean age 57	Only adverse events related to withdrawals appear to have been reported. 1. No 2. NR	1 acute MI in PBO group	1. Enriched for cardiac risk factors due to diabetes and/or metabolic syndrome, but younger age group 2. No major CV risk imbalances noted: Age (57-58), smokers (20%), BMI (30-31), DM (30%), antihypertensive (60-65%), statin (20-25%), and metformin (37-40%) were fairly balanced 3. Four patients discontinued (8%) --3 in T group due to HCT>52% and the one MI in placebo group.	Younger group, but enriched for CV risk factors <u>Strengths:</u> Long trial duration. <u>Limitations:</u> 1. Overall adverse event count and discontinuation rate not clear. Only adverse events related to withdrawals noted. 2. Unclear how adverse events were monitored during open-label extension 3. CV/safety outcomes not prespecified; unclear if blinded
1. Basaria, 2010 2. U.S. 3. Testosterone and placebo gel provided by Auxilium.	1. 6 months 2. 100mg topical testosterone gel daily (potential dose adjustment at 2 weeks)	1. TRT n=106; PBO n=103 2. IC: 65+ years, community-dwelling with mobility limitations, total serum T 3.5-12.1 nmol/l or free serum T <50pg/ml	Data and safety monitoring board reviewed serious adverse events as they occurred and cumulative adverse events q 6 months.	<u>Testosterone Group:</u> • Acute coronary syndrome and chest pain • Syncope (2) • Myocardial	1. High prevalence of chronic disease, pre-existing CV disease, and CV risk factors 2. Stratified by age (65-75 and 75+) before randomization. Balanced for age (74), BMI (30). Imbalance for race (more	Elderly frail group, high prevalence of pre-existing CV disease and risk factors <u>Strengths:</u>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
Various consulting fees and grant support from Auxilium and other pharmaceutical companies.		3. EC: Uncontrolled HTN, unstable angina, MI within 3 months, NYHA class III or IV CHF, active cancer, severe lower urinary tract symptoms, untreated severe sleep apnea, glucocorticoid or anabolic steroid therapy, HbA1c>8.5%, HCT>48%, PSA>4ng/ml, BMI > 40 4. Mean age 74	1. Yes 2. Yes	<p>infarction (2)</p> <ul style="list-style-type: none"> • Angioplasty and coronary artery bypass • Peripheral edema (5) • Ectopy on ECG • Left ventricular strain pattern during exercise testing • ST-segment depression during exercise testing • Elevated BP (2) • Atrial fibrillation with CHF exacerbation and hospitalization • Stroke • Elevated BP and atrial fibrillation • Tachycardia with fatigue • Death, suspected myocardial infarction • Congestive heart failure 	<p>blacks in T group). Higher % with dx hyperlipidemia on statin in T group (p 0.03). NS higher proportion with pre-existing CVD in T group (53% vs 47% in PBO group). Balanced for other CV risk factors (DM, BP, obesity, smoking) and Framingham risk score -22 in T group v.s 21 in placebo (p=0.31)</p> <p>3. Study stopped early due to increased CV-related adverse events in treatment group. Adherence > 90% both groups</p>	<p>1. Exhaustive reporting of CV-related events.</p> <p>2. Attempt to verify CV-related events through medical record review and exam</p> <p><u>Limitations:</u></p> <p>1. Randomization failure? Multiple imbalances in CV risk factors (but perhaps not enough to account for large imbalance in CV outcomes)</p> <p>2. CV events very broadly defined, unclear whether some were CV-related at all</p> <p>3. Early stopping may exaggerate magnitude of difference in CV events in TRT vs. PBO groups.</p> <p>4. Unclear if results generalizable to group expected to use T.</p>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
				<p>exacerbation</p> <p><u>Placebo group:</u></p> <ul style="list-style-type: none"> • Syncope resulting in hospitalization • Tachycardia • Elevated BP • Arrhythmia – ectopy noted on ECG before exercise testing • Carotid bruit and carotid-artery plaque identified on ultra-sonography 		

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Brockenbrough, 2006 2. U.S. 3. Yes (Auxilium)	1. 6 months 2. 100 mg topical T gel daily	1. TRT n=19; PBO n=21 2. IC: Male 18+ years old; hemodialysis-dependent ESRD; total T \leq 10.4 nmol/L; anemia requiring rHuEPO for \geq 3 months. 3. EC: T therapy within 6 months; use of anabolic supplements or medications that interfere with T; PSA > 4ng/mL; prostate CA, bilateral nephrectomy, liver failure, HIV, substance abuse, life expectancy < 6 months, home dialysis, or weight > 300 lbs; non-English-speaking; recent investigational study drug use; allergy/hypersensitivity to T gel components. 4. Mean age = 53 years (PBO), 59 (TRT)	Adverse events reported in detail on case-report forms throughout the study. 1. No 2. NR	<u>Withdrawals</u> <ul style="list-style-type: none"> 3 withdrawals due to CV death in TRT group 1 withdrawal due to stroke death in PBO group Withdrawals due to prolonged hospitalization in both groups—reason not specified. <u>Adverse events:</u> <ul style="list-style-type: none"> Access thrombosis: 6 PBO, 2 TRT Cardiac disorders: 3 PBO, 7 TRT 	1. Likely enriched for CV risk due to ESRD (suggesting high prevalence of DM and HTN, although prevalence of baseline comorbidities not reported) 2. Some group imbalances: mean age older (59 vs. 53, p=0.25), mean time on dialysis longer (44 vs. 32 months, p=0.49), baseline rHuEPO dose lower, and DHT and estradiol levels higher (p=0.02 and 0.01, respectively) in TRT group. 3. 45% discontinuation at 6 months. 71% of study attrition in TRT group was in first 3 months, compared to 30% in PBO group. Monthly drug compliance better in TRT group (76-94%) than PBO group (61-84%)	Younger group, but likely enriched for CV risk factors due to ESRD, which is associated with high prevalence of HTN and diabetes <u>Strengths:</u> 1. Systematic collection of adverse event and withdrawal data <u>Limitations:</u> 1. “Cardiac disorders” not further specified. 2. High discontinuation rate (45%), with earlier discontinuation in TRT group. 3. Prevalence of baseline comorbidities and CV risk factors not reported
1. Caminiti, 2009 2. Italy 3. No	1. 12 weeks 2. 1000 mg T undecanoate IM at 6 and 12 weeks	1. TRT n=35, PBO n=35 2. IC: Elderly males with symptomatic CHF (NYHA class II or III), LVEF < 40%; clinical stable without CHF hospitalization past 3 months 3. EC: Unstable angina or recent	Patients followed clinically every month. Echo and exercise ECG at baseline and end of study 1. No	Worsening CHF in 2 TRT patients (1 requiring hospitalization) and 1 PBO patient No side effect requiring	1. Elderly, pre-existing CHF suggests high baseline risk for CV-related events. Most were on beta-blockers, ACE-I, statin, and anti-platelets 2. TRT group slightly older (median age 71 vs. 69, NS). Co-	Enriched population: Elderly with stable pre-existing cardiac disease. Hypogonadism not required for study inclusion. <u>Limitations:</u>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		acute MI, history of severe liver or kidney disease, uncontrolled hypertension, significant pulmonary disease, HCT>50%, prostate CA, PSA>3ng/ml, severe lower urinary tract symptoms, vascular or other disease of lower extremities that could prevent a symptom limited exercise test 4. Median age 70 years; (range 66-76)	2. NR	discontinuation of treatment occurred, and there were no deaths.	morbidities and CV risk factors were fairly balanced. 3. 9% discontinuation overall--4 discontinued in TRT group, 2 in placebo, all "unrelated to treatment"	1. Short study duration 2. Unclear whether all CV adverse effects were reported or only those related to CHF exacerbation

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Chapman, 2009 2. Australia 3. Yes, Supported by Organon	1. 1 year 2. Oral T undecanoate 80 mg BID (Dose adjusted for HCT>54% or elevated PSA) Active placebo: nutritional supplement	1. TRT n=6 PBO n=6 years (men and women but only data for men described here) 2. IC: Age \geq 65, community dwelling, undernourished (Mini Nutritional Assessment score <24 and BMI <22 or self-reported weight loss \geq 7.5% in past 3 months) 3. EC: Inability to comply, cognitive impairment, HCT>50%, history of prostate CA, elevated PSA, abnormal prostate exam, breast CA, depression, CHF NYHA class III or IV, abnormal LFTs, predicted death within 1 year, any androgen therapy past 4 months 4. Mean age in men: 74 (TRT), 78 (PBO)	Hospitalizations reported by patients, confirmed by GP and, where possible, hospital records. Phone calls every 2-4 weeks, and home visits q 1-2 months, where adverse events occurrence was actively sought. 1. No 2. NR	1 MI in nutritional supplement only group (PBO) 1 MI death in T group (known heart disease) and no CV deaths in PBO group	1. Co-morbidities and CV risk factors not specified. 2. PBO group older (NS). Co-morbidities and CV risk factors not reported by study group 3. 35% reduced or discontinued treatment (men and women combined, study arm not specified) Adherence 83% overall while on treatment.	Frail elderly, but prevalence of CV risk factors and comorbidities not clear. Hypogonadism not required for study inclusion. <u>Strengths:</u> 1. Attempt to verify hospitalizations 2. Long study duration <u>Limitations:</u> 1. Unclear whether TRT MI death in study the same that the author reported? 2. Extremely small sample 3. Gender and study arm specific discontinuation not reported. 4. Limited generalizability: elderly frail/malnourished.
1. Copenhagen study, 1986 2. Denmark	1. 36 months intervention but only 8 to 62 months follow-up (median	1. TRT n=134; PBO n=87 2. IC: Hospitalized men with >50gm/day ethanol consumption for \geq 2 years and recent diagnosis	Clinical assessment at entry and during follow-up.	<u>Deaths in TRT group</u> • 12 bleeding esophageal varices	1. Comorbidities other than liver-related were not specified. CV risk factors not reported. 2. Unknown how well groups	Younger group, all with advanced alcoholic liver disease. Hypogonadism not required for study inclusion.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
3. Not stated	28 months) due to death and early stopping of study 2. Micronized-free T 200mg TID	of cirrhosis without other known cause 3. EC: Unable to cooperate, HbsAg+, malignancy, Klinefelter's syndrome, recent treatment with anabolic-androgenic steroids 4. Mean age 53 (range 24-79)	1. No 2. Outcome assessors blinded, but not clear if cause of death determination was blinded	<ul style="list-style-type: none"> 1 acute MI 1 hepatic vein and 2 portal vein thrombosis <u>Deaths in PBO group</u> <ul style="list-style-type: none"> 5 bleeding esophageal varices <p>1 patient in TRT group discontinued due to acute MI, unclear if this was same patient who died from acute MI</p> <p>In 12% (TRT) and 18% (PBO), cause of death was unknown.</p>	balanced in CV risk factors 3. 11% (TRT) and 9% (PBO) discontinuation rate. Study stopped early because of increased mortality seen at provisional comparison based on 184 patients.	<u>Strengths:</u> 1. Long study duration (but highly variable length of follow-up) with reasonably good retention rate <u>Limitations:</u> 1. Very limited generalizability—all patients with alcoholic cirrhosis, likely to have atypical baseline hematologic and coagulation parameters. 2. Only deaths reported. Unclear if other CV-related events occurred, and unclear if cause of death was determined by blinded assessor. 3. Baseline androgen status and CV risk factors not described
1. Emmelot-Vonk, 2008 2. Netherlands 3. No (trial medication provided by	1. 6 months 2. 80mg T undecenoate orally BID	1. TRT n=120; PBO n=117 2. IC: Aged 60-80 years, T level <13.7nmol/L (50% percentile) 3. EC: MI or CVA past 6 months, symptomatic CHF; malignancy past 5 years or history of	AEs information sought by questioning and examining patients 1. AEs and serious	"Cardiovascular complaints:" 7 (6%) in TRT group, 3 (3%) in PBO group 5 serious AEs in TRT group, 10 in PBO group: 5 planned	1. Half with prior CV disease, including MI (>6 months prior), angina, HTN, or stroke. Diabetes and symptomatic CHF excluded. HTN not well-controlled—mean baseline SBP > 150	Older group, with high prevalence of pre-existing CV disease (including HTN), but diabetes and CHF excluded. <u>Strengths:</u>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
Organon)		hormone-dependent tumor, serious liver/renal disease, HCT \geq 50%, epilepsy, migraine $>$ 1/month, diabetes, fasting glucose $>$ 6.9mmol/L, corticosteroid use past 6 months (except short courses or inhaled), use of testosterone/androgens, history of prostate hyperplasia, elevated PSA 4. Mean age 67	AEs were prespecified 2. Outcome assessor blinded	hospitalization, additional hospitalizations "not related to the study medication," and 2 prostate CA	2. 17.5% smokers in TRT vs. 12.8% in PBO group. Mean SBP and DBP higher in TRT group. 3. 13% (TRT) and 12% (PBO) discontinuation rate . 7 in each group with no follow-up. Adherence: $>$ 90% of patients used at least 80% of medication. Blinding was effective.	1. AEs and serious AEs prespecified and ascertainment blinded 2. More broadly generalizable group than many other studies. <u>Limitations:</u> No detail given about nature of "cardiovascular complaints," whether any verification was done, or which hospitalizations were CV-related
1. English, 2000 2. UK 3. Not stated (SKB provided patches)	1. 12 weeks 2. 5mg topical T nightly (two 2.5mg transdermal patches)	1. TRT n=25; PBO n=25 2. IC: Coronary artery disease ($>$ 70% stenosis of a major coronary artery by angiography, previous proven MI, or typical angina symptoms and a "double positive" [$>$ 1mm downsloping ST-segment depression with chest pain on exercise stress test]) 3. EC: Elevated PSA or other contraindication to androgen therapy, left main (or equivalent stenosis), coronary or cerebrovascular event 4. Mean age 62	1. Only the treadmill results were prespecified 2. Treadmill analysis was blinded, not clear if adverse event assessment was blinded	1 patient in TRT group had MI (while awaiting coronary revascularization) 2 patients withdrawn from TRT arm: 1 with MI, one with elective coronary angioplasty	1. High risk population with known coronary artery disease 2. Baseline imbalances, with more PBO patients with HTN, DM, family history, current smoking (16 vs. 4%), hypercholesterolemia, use of ACE, diuretic, and Nicorandil (an anti-anginal), baseline time to 1mm ST-segment depressions 3. 12% discontinuation from TRT arm, for MI, skin irritation, and early coronary angioplasty	Younger group but highly enriched, all with pre-existing CV disease. Hypogonadism not required for study inclusion. <u>Limitations:</u> 1. Failed randomization with regard to risk of CV event? (apparent higher risk in PBO group) 2. Short trial duration 3. Unclear whether MI noted in safety section and in withdrawal description was same event

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Hall, 1996 2. UK 3. Yes, supported by Schering Healthcare.	1. 9 months 2. 250 mg T enanthate IM monthly, increased after 6 months to q 2 weeks	1. TRT n=17, PBO n=18 2. IC: Receiving stable dose of routine anti-rheumatic therapy 3. EC: Contraindications to T 4. Median age 62 (range 34-79)	CV-related adverse events noted only as reason for withdrawal 1. No 2. NR	1 cerebrovascular accident and 1 hypertension in PBO arm	1. 89% current or ex-smokers. Otherwise, baseline CV risk not well characterized. 2. TRT group was older (NS, mean 64 vs. 59 yrs) and lower weight (p=0.05) 3. 12% discontinuation from TRT arm for osteomyelitis, pneumonia; 17% discontinuation from PBO arm, due to HTN, moved, cerebrovascular accident	Younger group, all with rheumatoid arthritis, High prevalence past/current smoking. Hypogonadism not required for study inclusion. <u>Strengths:</u> Relatively long study duration <u>Limitations:</u> 1. Only AEs resulting in withdrawal were described 2. Very small sample size 3. Limited generalizability—only rheumatoid arthritis patients

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Ho, 2011 2. Malaysia 3. Yes, supported by Bayer Schering	1. 48 weeks 2. T undecanoate 1000mg IM at weeks 0, 6, 18, 30, and 48	1. TRT n=60; PBO n=60 2. IC: Age 40-70 years, total T <12 nmol/L and total Aging Male Symptoms (AMS) score ≥ 27 , PSA <4ng/ml 3. EC: HbA1c >8%, clinical hypo or hyperthyroidism; HCT >55%, prostate or male mammary CA, liver tumors, other significant medical conditions (American Society of Anaesthetists score >3), psychosis, schizophrenia, or manic depression, or sleep apnea, hypersensitivity to active substance or on medication interfering with T metabolism or recent T treatment 4. Mean age 53 (range 40-70)	Safety monitored by scheduled assessment and self-report of adverse events. 1. No 2. Unblinded: codes were revealed when a serious adverse event occurred	<u>TRT group:</u> 1 death (MI) 1 withdrawal for chest pain <u>PBO group:</u> 1 death (MI) 1 withdrawal for chest pain Both patients with MI had history of ischemic heart disease. Both chest pain withdrawals refused further investigation	1. Relatively younger and lower risk group for CV events (significant medical conditions excluded) 2. Baseline CV risks were somewhat unbalanced with TRT group having higher baseline risk: heavier, more HTN and higher BP at baseline, higher diabetes prevalence, more history of coronary artery disease, AMS score higher (NS) 3. 7% (TRT) and 4% (PBO) discontinuation rate	Overall, younger and healthier group. <u>Strengths:</u> Relatively long study duration <u>Limitations:</u> 1. Randomization failure?—groups not well balanced for risk factors. 2. Only deaths and withdrawals described, not other AEs, and no adjudication or medical verification of cause of “chest pain”
1. Hoyos, 2012 2. Australia 3. Yes, Bayer Schering	1. 18 weeks 2. T undecanoate 1000 mg at 0, 6, and 12 weeks All underwent weight loss program	1. TRT n=33; PBO n=34 2. IC: Aged 18+ years, male, BMI >30kg/m ² , and apnea hypopnea index >10. 3. EC: uncontrolled concurrent medical or psychiatric illness, CPAP need or more severe sleep apnea, medication altering androgen action sleep or body weight, contraindications to T or	Clinical assessments at 0, 6, 12, 18 weeks. Safety follow-up visit at 26 weeks. 1. No 2. “Randomization code not broken until all data were collected and	1 cardiac event in TRT group, 0 in PBO group	1. Pre-existing CV disease in 3 participants (2 in PBO, 1 in TRT) 2. CV/metabolic risk factors well balanced except waist circumference (significantly higher in PBO group) 3. 21% (TRT) and 18% (PBO) discontinuation rate. Only 1 withdrawal for AE in each	Younger, healthier group with lower baseline CV risk. Hypogonadism not required for study inclusion. <u>Strengths:</u> Maintained blinding <u>Limitations:</u>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		injection, desire for paternity next 12 months or in sport banning testosterone, HCT > 52%, PSA, > 4 ng/ml, in another drug trial past 30 days 4. Mean age 48 (TRT), 49 (PBO)	database locked."		group.	1. "Cardiac event" not specified or verified
1. Jones, 2011 2. Europe (multiple countries) 3. Yes, sponsored and funded by ProStrakan.	1. 6 months (+ 6 months open label extension) 2. 60mg T gel topically (2% gel) daily	1. TRT n=108, PBO n=112 2. IC: Men aged 40+ years with total T ≤ 11 nmol/L or free T ≤ 255 pmol/L, 2+ symptoms of hypogonadism, and Type 2 diabetes and/or metabolic syndrome 3. EC: T treatment past 6 months, hormone therapy past 3 months, prostate/breast CA, abnormal prostate exam, severe BPH or elevated PSA. 4. Mean age: 60	AEs elicited each visit by a "non-leading question" 1. No 2. "All individuals involved in monitoring, data management, or other study aspects were blinded to treatment"	Cardiovascular AEs occurred more commonly with PBO than TRT (10.7% vs. 4.6% p=0.095) 1 cardiovascular death (PBO)	1. Elevated CV risk due to DM and metabolic syndrome 2. Groups balanced for reported cardiac risk factors 3. 29% discontinuation from RCT phase, not broken out by study arm. "Safety population comprised all randomized patients who received ≥ 1 dose of study medication." Nine patients lost to follow-up.. 18 withdrawals due to AEs in TRT group and 12 in PBO group. Substantial cross-over occurred (protocol violations in 125 participants)	Younger group but enriched for CV risk <u>Strengths:</u> Larger study, groups balanced for reported CV risk factors <u>Limitations:</u> 1. CV AEs not further specified 2. High drop out and cross-over rate could create bias. Unclear what drug was actually being taken among those with CV-related AEs. 3. AE numbers not given, only %'s—numbers back-calculated by Xu.
1. Kalinchenko, 2010 2. Russia	1. 30 weeks 2. 1000 mg T IM at 0, 6, and 18 weeks	1. TRT n=113, PBO n=71 2. IC: Men aged 35-70 years with metabolic syndrome and total T <12.0 nmol or free T <225 pmol.	Safety data based on reasons for discontinuation of intervention	1 angina case and 1 MI death in PBO group	1. Relatively high risk for CV disease due to metabolic syndrome. 23-25% current smokers, 28-34% T2DM, 86-	Relatively high-risk group but unknown prevalence of pre-existing CV disease

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
3. Yes, supported by Bayer Schering	All received diet and physical activity education	3. EC: participation in another clinical study, incapable of consenting or complying, serious organic or mental disease, known or suspected prostate/breast CA, hepatic tumors or disease, renal disease, HCT>55%, hypersensitivity to study drug. 4. Mean age 51.6 (TRT), 52.8 (PBO)	1. No 2. NR		89% on BP lowering drugs 2. Baseline characteristics balanced. 3. 7% (TRT) and 8% (PBO) discontinuation rate. 1 LTFU in TRT group	<u>Strengths:</u> Good retention <u>Limitations:</u> No detail on CV-related outcomes or whether there were other CV AEs in those not discontinuing treatment
1. Kaufman, 2011 2. U.S. 3. Yes, funded by Abbott	1. 182 days 2. Topical T gel: 1.25, 2.5, 3.75, and 5g daily Dose adjustments on days 14, 28, and 42.	1. TRT n=214; PBO n=37 2. IC: Men ages 18-80 years with total T <300 ng/dL and BMI between 18 and 40 kg/m ² 3. Impaired liver function, prostate symptoms, PSA > 2.5 ng/ml, abnormal prostate exam, untreated prolactinoma, known or suspected prostate or breast CA, eczema, psoriasis, sleep apnea, multiple sclerosis, skin disease, heart failure, HCT>48% or HGB >16 g/dL. 4. Mean age 53.5 (TRT) and 55.5 (PBO)	ADs and vital signs recorded throughout study. ECGs at baseline and day 182. 1. No 2. NR	19 CV-related events were recorded in 23 patients: <u>TRT group:</u> cardiac failure congestive, cardiomyopathy, myocardial infarction, palpitations, tachycardia, chest pain, edema peripheral, pitting edema, BP decreased, BP increased, ultrasound Doppler abnormal, joint effusion, dizziness,	1. Low-risk group except mean BMI>30. 2. Mean BP balanced at baseline. No information on other CV risk factors. 3. 28% (TRT) and 30% (PBO) discontinuation; 25 withdrawals due to AE in TRT group (most for PSA increases). 5 LTFU in TRT group and 2 in PBO group. Subjects included in the safety sample were those allocated to treatment having at least one dose of study medication	Hypogonadal but otherwise healthy men. Younger group. <u>Limitations:</u> 1. High number of discontinuations in both groups. 2. Difficult to be confident actual number of CREs—discrepancies between text and tables. Xu used conservative estimate (from table). Text implies that other CREs occurred in both the TRT and PBO groups, but not entirely clear. Author did not respond to inquiries. 3. No relation described between dose and CV-related AEs.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
				<p>syncope vasovagal, hypertension, malignant hypertension, and phlebitis</p> <p><u>PBO group</u>: presyncope, nocturia</p> <p>Table notes 11 vascular treatment emergent AEs and 6 HTN cases in TRT group, 0 in PBO group</p> <p>Text notes severe TEAEs in 11/234 subjects the TRT group and none in the PBO group—list MI and tachycardia. 16 different severe TEAEs are listed.</p>		
1. Kenny, 2004 2. U.S. 3. No	1. 12 weeks 2. 200 mg T enanthate IM every 3 weeks	<p>1. TRT n=6; PBO n=5</p> <p>2. IC: Men aged 65+ years with bioavailable T level <128 ng/dl and mild-moderate cognitive impairment</p> <p>3. EC: History of prostate CA, nodule or elevated PSA, HGB.16.5 gm/dL, vitamin E use</p> <p>4. Mean age 81 (TRT); 78 (PBO)</p>	<p>Safety ascertainment not specified</p> <p>1. No 2. No</p>	1 cerebral vascular accident in PBO group	<p>1. 2 with history of heart disease in TRT group, 1 in PBO group, 2 in each group on cholesterol-lowering therapy; 1 with HTN in TRT group, 2 in PBO group</p> <p>2. Very small sample, groups not entirely balanced in cardiac history and risk factors.</p> <p>3. No discontinuations</p>	<p>Very elderly, with cognitive decline</p> <p><u>Limitations</u>:</p> <p>1. Extremely small sample</p> <p>2. Short duration</p>

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Legros, 2009 2. 14 European countries 3. Yes, Schering-Plough	1. 12 months 2. .80, 160, or 240 mg/day oral T undecanoate	1. TRT n=78 (80mg), 82 (160mg), 77 (240mg); PBO n=79 2. IC: Men age 50+ years, BMI between 18 and 34 kg/m ² with symptoms of androgen deficiency (ADAM questionnaire) and free T <0.26 nmol/L 3. EC: Prostate/breast CA, abnormal prostate exam, lower urinary tract symptoms, PSA >4 ng/ml, cause of androgen deficiency other than aging, androgen/anabolic steroid treatment past 2 years, hyperprolactinemia or treatment with prolactin-lowering drugs, history polycythemia or HCT>50%, severe sleep apnea, uncontrolled HTN, insulin-dependent DM, clinically significant baseline lab values, untreated endocrine disorders, liver or renal disease, psychiatric disease, history or presence of other disorders such as clinically significant CV, cerebrovascular, or hematological disorders which could compromise participation, medication that could interfere	Follow-up included questioning patients about adverse events, and exam—unclear frequency 1. No 2. NR	1 TRT group death due to arrhythmia and hypertrophic cardiomyopathy (not related to study drug as judged by investigator) 1 TRT group death 3 months after end of treatment due to cardiac arrest (not related to study drug as judged by investigator) 19 other patients with “serious AEs” not otherwise specified (2 in placebo group)—higher proportion in TRT group	1. Apparently healthy group based on exclusion criteria but no information on baseline CV risk factors. 2. Groups balanced in general but minimal info on CV risk factors 3. 25% discontinuation rate without marked difference between groups in rate or reason for discontinuation.	Younger group, many exclusions suggest healthier participants <u>Strengths:</u> 1. Large study of long duration 2. Fairly broadly generalizable to younger, healthier populations (although non-US) <u>Limitations:</u> 1. Only deaths reported by treatment group. Higher proportion of serious AEs in TRT group compared to PBO not further specified whether any were CV-related. 2. Fairly high discontinuation rate (but balanced) 3. Minimal information on baseline CV risk of group

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		with T 4. Mean age 58.7				
1. Malkin, 2006 2. UK 3. No (patches provided by Watson)	1. 12 months 2. 5mg transdermal T patch daily	1. TRT n=37, PBO n=39 2. IC: Ambulatory males aged 18+ years with stable CHF >6 months and impaired exercise tolerance and at least moderate LV systolic dysfunction on echo. 3. EC: Use of sex hormones, abnormal PSA, exercise limitation due to non-cardiac cause, malignancy. 4. Mean age 63.1 (TRT), 64.9 (PBO)	Safety monitoring plan not described 1. No 2. No	<u>TRT group:</u> 1 stroke 1 unstable angina 1 presyncope 2 exacerbation CHF <u>PBO group:</u> 2 new arrhythmia 1 sudden death 1 presyncope 2 exacerbation CHF	1. Elevated cardiac risk due to CHF 2. Randomization stratified by ischemic vs. non-ischemic etiology of heart failure—balanced across groups. Mean resting pulse higher in TRT group, otherwise fairly balanced. More smokers (10) in TRT group than PBO (6) but NS. Slightly more DM in PBO group (8 vs.5), also NS. 3. 49% (TRT) and 41% (PBO) discontinuation	All patients with stable CHF—elevated risk for CV events Most participants without hypogonadism: only 24% with baseline T below normal range <u>Limitations:</u> 1. No significant change in either HCT or PSA—lower dose? 2. Very high drop-out rate—many due to skin reactions.
1. Marin, 1993 2. Europe (country?) 3. Yes, Besins-Iscovesco	1. 9 months 2. Testogel 125 mg topically daily ; second group with 125 mg dihydrotestosterone topically daily	1. 31 men total (3 groups) 2. IC: Men >40 years and abdominally obese (waist-hip ratio>0.9), BMI <35 kg/m ² , total T < 20nmol/L and <2 kg weight change in past 2 months. 3. EC: Prostate enlargement and/or elevated PSA. Clinical DM or HTN requiring drug treatment, suspected alcohol abuse 4. Mean ages: 56.7 (TRT 1), 57.8	Monthly history and physicals 1. No 2. No	1 splanchnic venous thrombosis in TRT group (had had similar problems prior to study)	1. DM and HTN excluded but all with increased waist-hip ratio, increasing CV risk 2. TRT groups were slightly heavier than PBO but slightly younger. No major imbalances. 3. 4 discontinued, 3 for “occupational reasons”	Younger group with abdominal obesity, but major risk factors of DM and HTN excluded, others not described. Low-normal baseline T levels included. <u>Limitations:</u> 1. Very small sample 2. Only withdrawals were noted, not all AEs.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		(TRT 2), 58.5 (PBO)				
1. Merza, 2006 2. UK 3. Yes, Ferring Pharmaceuticals	1. 6 months (with 6 month open label extension) 2. 5mg/day transdermal patch	1. TRT n=20; PBO n=19 2. IC: Men >40 years with total testosterone <10nmol/L presenting to a male sexual dysfunction clinic 3. Prostate/breast CA, BPH, PSA>2.5, uncontrolled HTN, DM, uncontrolled cardiac disease, renal failure, liver disease, HCT>50%, history of aggressive behavior, alcohol or drug abuse, anticoagulant therapy, testosterone replacement 4. Mean age 63 (TRT) and 59.7 (PBO)	Baseline and f/u visits at 1, 3, 6, 9, 12 months with exam and labs. 1. No 2. NR	1 patient withdrawal in PBO group due to angina	1. Younger group, DM and uncontrolled HTN or cardiac disease excluded. Other CV risk factors not described. 2. TRT group older, other risk factors not described 3. In RCT phase, 1 PBO withdrawal. in open-label extension, 3 TRT and 1 PBO withdrawal due to elevated HCT and 1 TRT and 2 PBO withdrawals with no specific cause	Younger, apparently healthier group. Little information on CV risk factors but DM and uncontrolled HTN excluded. <u>Limitations:</u> 1. Only withdrawal information given. 2. Small study, with little description of baseline CV risk factors.
1. Nair, 2006 2. U.S. 3. No, but various consultant fees etc.	1. 2 years 2. 5 mg transdermal T patch daily	1. TRT n=30; PBO n=31 (only men included) 2. IC: Age 60+ years, bioavailable testosterone < 3.6 nmol/L and DHEA level < 2.6 micromol/L 3. EC: Clinically important coexisting illnesses or conditions that could have an effect on outcomes measures, elevated PSA or abnormal prostate exam. 4. Mean age 66.2 (TRT), 67.1 (PBO)	"Adverse effects were assessed" 1. No 2. No	5 CV AEs in testosterone group, 5 in PBO group.	1. Older men, but many co-existing illnesses and conditions appear to have been excluded. 2. Groups fairly well balanced for age, BMI, lipids, fasting glucose 3. 10% (TRT) and 0% (PBO) discontinuation 3 LTFU in TRT group, 1 in PBO group. 24/30 completed on protocol in TRT group and 28/31 in PBO group	Generally healthy older men with low or low-normal testosterone. <u>Strengths:</u> 1. Long duration 2. Tables of adverse events included <u>Limitations:</u> 1. Exclusion criteria not clearly elucidated.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
						2. Details of CV AEs not provided 3. Fairly high proportion of discontinuation and treatment cross-overs
1. Sih, 1997 2. U.S. 3. Funding source not stated	1. 12 months 2. 200 mg T cypionate IM q 14-17 days	1. TRT n=17, PBO n=15 2. IC: Men 50+ years; community dwelling; Mini mental status exam score >23; normal liver function tests, PSA, HCT; bound testosterone level ≤ 60 ng/dL. 3. EC: Significant prostate disease, COPD, CHF or angina 4. Mean age 65 (TRT), 68 (PBO)	Not specified. 1. No 2. NR	1 TRT group withdrawal for uncontrolled A fib with CHF 1 PBO group withdrawal due to stroke	1. Medical conditions (TRT/PBO): HTN 4/2, DM 2/1, hypercholesterolemia 2/1, atrial fib 2/0, depression 2/0, s/p CABG no angina 0/1, on aspirin 7/4. TRT group slightly older. 2. Low numbers, but slightly more TRT than PBO with HTN, DM, A fib. 3. TRT group: 14/15 completed 6 months, 12/15 completed 12 months; 1 LTFU before 6 month eval and 3 withdrawals for HCT >51% PBO group: 14/17 completed 6 months, 10/17 completed 12 months. 1 LTFU before 3 month eval, 1 LTFU before 9 month eval.	Older group, with fairly low prevalence of CV-related disease and risk factors. <u>Limitations:</u> 1. Very small study 2. Only AEs associated with withdrawals reported
1. Snyder, 2001 2. U.S.	1. 36 months	1. TRT n=54; PBO n=54 2. IC: Men >65 years with	Obtained history of clinically apparent CV events q 6	<u>Testosterone-treated group:</u>	1. No major diseases as part of IC but EC also not extensive--not clear what co-morbidities	Older men with low-normal testosterone.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
3. Not stated. ALZA Corp. provided testosterone patches.	2. Testoderm scrotal patch 6mg/day	baseline T <16.5 nmol/L 3. EC: Diseases or medication known to cause hypogonadism or that testosterone could exacerbate such as prostate CA or BPH. 4. Mean age: 73 both groups	months and confirmed events with hospital records: events included MI, CABG, arrhythmia, and vascular events such as stroke and peripheral embolism 1. Yes 2. NR	2 MI 2 CABG 3 arrhythmia 2 other vascular events TOTAL 9 <u>PBO-treated group:</u> 1 MI 2 CABG 1 arrhythmia 1 other vascular event TOTAL 5 RR 1.8 (0.7-5.0)	were present in study population or by study arm 2. LDL higher in PBO group (NS). Age balanced. 3. 7% (TRT) and 15% (PBO) discontinuation	<u>Strengths:</u> CV events were specifically sought, prespecified and verified through medical records, but not clear whether blinded. <u>Limitations:</u> 1. Inclusion and exclusion criteria not specifically listed. Baseline CV risk and health status of study population not clear. 2. Some difference in discontinuation rate—possibly informative censoring
1. Spitzer, 2012 2. U.S. 3. No	1. 14 weeks 2. T 1% gel 10 g, increased to 15 mg after 2 weeks if serum T <17.35 nmol/L (all participants also got sildenafil)	1. TRT n=70, PBO n=70 2. IC: Men aged 40-70 years, erectile dysfunction, serum T <11.45 nmol/L or free T <50 pg/mL 3 EC: Prostate /breast CA, penile abnormalities, lower urinary tract symptoms, untreated sleep apnea, major psychiatric disease, HCT >50%, elevated creatinine or PSA, HbA1C ≥ 8.5%, BP> 160/100,	Adverse events were ascertained at each visit. 1. No 2. "Investigators and study staff did not have access to the randomization table"	4 (6%) with CV AE in TRT group, 2 (3%) in PBO group	1. 21-22% with DM, 40-45% with HTN, 46-50% with CV disease, mean BMI 32. 2. Groups fairly balanced. TRT with NS higher proportion with CV disease and HTN. 3. 14% (TRT) and 17% (PBO) discontinuation; with 5 LTFU (TRT) and 11 LTFU (PBO). Adherence 90% TRT, 89% PBO	Younger men, but with high baseline risk for CV event (half with pre-existing CV disease) Trial was of sildenafil and testosterone combined or sildenafil alone. <u>Limitations:</u> 1. Short trial duration 2. No detail given on CV AEs

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		MIR or stroke in past 6 months, uncontrolled heart failure, using androgens or nitrates 4. Mean age 55.1 (TRT), 54.6 (PBO)				3. Both TRT and PBO groups received drug that also has CV effects.
1. Srinivas-Shankar, 2010 2. U.K. 3. Yes, funded by Bayer Schering	1. 6 months 2. 50mg/day 1% transdermal T gel. Dose adjusted at 3 months.	1. TRT n=138, PBO n=136 2. IC: Men aged 65+ years, community-dwelling, meeting 1+ criteria for frailty and T ≤12 nmol/L 3. EC: Prostate CA, BPH, high PSA, chronic renal impairment or active liver disease, moderate-severe PVD, CHF (NYHA class >1), angina requiring nitrates >once a week, untreated sleep apnea, major psychiatric illness, medications interfering with sex steroid metabolism, stroke with persistent weakness, active muscle/joint disease, cognitive impairment. 4. Mean age 74 (both groups)	1. No 2. "Monitoring clinician" remained blinded	<u>TRT group</u> 1 pulmonary embolism 1 heart failure 1 abdominal aneurysm 1 constrictive pericarditis <u>PBO group</u> 1 acute MI 1 death from ruptured AAA	1. Average of 2.5-2.6 comorbidities, not otherwise specified 2. Age, weight, BMI, frailty scores, cholesterol levels balanced 3. 11% discontinuation overall, study arm not specified. Compliance assessed by self-report. Over 85% used more than 95% of study medication, with no significant differences between groups	Frail and "intermediate frail" elderly men with low to borderline-low testosterone. <u>Strengths:</u> 1. Large study, with good balance of comorbidities in study arms 2. Maintained blinding of monitoring physicians 3. Assessed medication compliance—no major imbalances 4. Long study duration, with reasonable retention <u>Limitations:</u> 1. No detail on discontinuations by study arm 2. Limited description of CV risk factors

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Svartberg, 2004 2. Norway 3. No	1. 26 weeks 2. 250 mg T enanthate IM q 4 weeks	1. TRT n=15; PBO n=14 2. IC: Men aged 54-75 years with moderate-severe COPD, stable medical condition 3. EC: Asthma, malignancies, cardiac impairment, hepatic or endocrine disease 4. Mean age 64.5 (TRT, range 54-74); 67.5 (PBO, range 56-75)	Potential adverse events were recorded every fourth week. 1. No 2. NR	1 PBO patient died of probable MI (sudden death).	1. High prevalence past/current smoking due to COPD but active cardiac and endocrine disease excluded. 2. Control group slightly older (NS) and higher BMI (NS). Smoking balanced. Other CV risk factors not described. 3. All completed to week 12, 7% discontinuation by week 26, study arm not specified	Men without known pre-existing CV disease but at elevated risk due to heavy smoking history (COPD). Hypogonadism not required for study inclusion. High baseline T levels (low T not a criterion for study inclusion) <u>Limitations:</u> 1. Very small sample 2. Limited description of CV risk factors 3. Limited generalizability—only men with COPD included
1. Svartberg, 2008 2. Norway 3. Yes, Bayer Schering	1. 1 year 2. 1000mg T undecanoate at 0, 6, 16, 28, and 40 weeks	1. TRT n=19; PBO n=19 2. IC: Men aged 60-80 with testosterone ≤ 11.1 nmol/L 3. EC: Malignancy, unstable ischemic or congestive heart disease, epilepsy, migraine, HCT<50% or HGB >17gm/100ml, PSA>4, creatinine>130mmol/L, ALT >100 U/L, allergy to study medication, warfarin treatment, participation in other studies. 4. Mean age 69 both groups	Exams at baseline and 1 year 1. No 2. NR	1 death from cardiac arrhythmia in TRT group	1. 18-22% smokers, 4/19 (TRT) and 5/19 (PBO) with coronary heart disease, 1 in each group with T2DM, 4/19 (TRT) and 7/19 (PBO) with HTN 2. Groups fairly balanced for CV risk factors. 3. 1 withdrawal without reason from each study arm and 1 cardiac death in TRT group	Older group, but fairly low prevalence of coronary heart disease, DM, HTN, and smoking. <u>Strengths:</u> Long study duration <u>Limitations:</u> 1. Very small sample, but groups fairly well balanced for CV risk factors 2. Only deaths reported, unclear if other CREs occurred

Key: AE=adverse event; BPH=benign prostatic hypertrophy; CA=cancer; CABG=coronary artery bypass graft; CHF=congestive heart failure; CVA=cerebrovascular accident; ESRD=End stage renal disease ; HCT=hematocrit; HGB=hemoglobin; HTN=hypertension; LTFU=loss to follow-up; MI=myocardial infarction; NYHA=New York Heart Association; NR=not reported; NS=non-significant; PBO=placebo; PSA=prostate-specific antigen; PVD=peripheral vascular disease; T=testosterone; TRT=treatment

7.2 APPENDIX B: XU ET AL. ADDITIONAL FILE 2 AUTHOR CONTACTS

Additional file 2: Trials where authors were contacted for additional information and responses.

Author and publication year	Reason for contact	Date		Response	Action
		Contacted	Responded		
Kenny 2002 (Kenny et al., 2002; Kenny, Bellantonio, Gruman, Acosta, & Prestwood, 2002; Kenny, Prestwood, Gruman, Marcello, & Raisz, 2001)	We could not find any reports on this trial giving cardiovascular events in the “Safety” section or the reasons for discontinuation or withdrawal. This trial appears to be shown in a previous meta-analysis with testosterone therapy protecting against cardiovascular related events.(Calof et al, 2005) Given the trial had 34 in the T group and 33 in P group, this is equivalent to 0 cardiovascular events in the T group and 6 in the P group.	30 January 2012 10 Feb 2012	No		Study excluded because events inferred from another meta-analysis not confirmed by author
Steidle 2003 (Steidle et al., 2003)	Two cardiovascular events are described in the T group (hypertension and coronary artery disease) in a section on events in the treatment group. There is no similar information about the placebo group, so it is unclear whether there were also cardiovascular-related events in the placebo group.	13 January 2012 10 Feb 2012	No		Study excluded because unclear if events from placebo arm reported
Crawford 2003	The text describes 15 serious adverse events (SAEs) in a study of 51 men comparing nandrolone (17) to	12 December	Yes	The author replied that because the	Study excluded because

Author and publication year	Reason for contact	Date		Response	Action
		Contacted	Responded		
(Crawford, Liu, Kean, Bleasel, & Handelsman, 2003)	testosterone (18) to placebo (16). Of these SAEs, 11 were cardiovascular-related, i.e., myocardial ischemia (4), pulmonary embolism (2), rupture aortic aneurysm (2), carotid artery thrombosis (1) and cardiomyopathy (2). The text says there was significant difference among treatment groups in the distribution of SAEs. A previous meta-analysis shows this study as having what looks like 6 or 7 cardiovascular events in the T group and 0 in the P group. (Calof et al, 2005)	2011 02 February 2012		data was quite old, and in Australia people only have to keep the original data for 7 years, so he could not confirm the number of CVD events. (07 Feb 2012)	events inferred from another meta-analysis not confirmed by author
Sullivan 2005 (Sullivan et al, 2005)	“Exacerbation of his chronic obstructive pulmonary disease and a non-Q wave myocardial infarction 3 d after a high-intensity workout” Unclear as to study arm where this occurred.	30 January 2012 10 Feb 2012	No		Study excluded because unclear in which group event occurred.
Legros 2009 (Legros et al, 2009b)	The text describes 254 adverse events, but does not give a breakdown of adverse events or serious adverse events by study arm. The paper only gives deaths by study arm.	12 December 2011 10 February 2012	Yes	Transferred request at 15 Dec 2011 but no response afterward	Study included with deaths only
Chapman 2009 (Chapman et al.,	Deaths are not given by cause and study arm, only hospitalisations	30 January 2012	Yes	Author additionally reported one death from myocardial infarction in the	Study included

Author and publication year	Reason for contact	Date		Response	Action
		Contacted	Responded		
2009b)				testosterone arm.	
Kenny 2010 (Kenny et al., 2010)	The study flow chart gives 2 cardiac withdrawals in the testosterone group (CHF and leaky valve) and 4 cardiac withdrawals in the placebo group (open heart surgery, myocardial infarction, aneurysm and CHF). The 'Safety evaluation' section also gives 3 deaths from stroke without giving study arm. The same section also says that "Seven individuals withdrew from treatment for signs and symptoms consistent with cardiac disease, including myocardial infarction (n=2), congestive heart failure (n=3), and significant lower extremity edema (n=2)."	18 January 2012 10 Feb 2012	No		Study excluded because impossible to reconcile information from different parts of the paper.
Pugh 2004 (Pugh, Jones, West, Jones, & Channer, 2004)	The text describes "One patient in the active group was admitted to hospital with breathlessness after eight weeks of treatment", which seems like a cardiovascular disease but could not confirm.	12 December 2011 02 February 2012	Yes	Replied at 13 Dec 2011. Question not answered	Study excluded as diagnosis of event uncertain.
Kaufman 2011 (Kaufman et al., 2011b)	The text says "19 cardiovascular-related events were recorded in 23 patients" without giving study arm, whilst the table of "Incidence of treatment-emergent adverse events in >2% of the subjects n (%)" gives 11 events under a heading of "Vascular disorders".	01 March 2012 08 March 2012	No		Study included using events recorded as "Vascular disorders"

Author and publication year	Reason for contact	Date		Response	Action
		Contacted	Responded		
Frederiksen (Frederiksen, Hojlund, Hougaard, Brixen, & Andersen, 2012) 2012	The text says “Two SAE occurred in two participants and included a single possible treatment-related event (venous thrombosis in the leg, hematocrit within the normal range) and a single non-related event (car accident).”	23 January 2013 04 February 2013	No		Study excluded as uncertain whether event occurred in placebo or treatment arm.

T testosterone, P placebo

Source: Xu et al., 2013, Additional File 2 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648456/>)

7.3 APPENDIX C: XU ET AL. ADDITIONAL FILE 3 QUALITY ASSESSMENT OF THE SELECTED PLACEBO-CONTROLLED RCTs OF THE EFFECTS OF TESTOSTERONE THERAPY ON CARDIOVASCULAR EVENTS (CREs).

Author and publication year	Randomization	Treatment allocation concealed	Group similarity	Eligibility listed	CRE Outcome assessor blinded	Care provider blinded	Subject masked	Point estimates and variability for outcome	ITT of main results	CRE definition pre-specified or assessed before study unblinded	Table showing CRE by study arm
The Copenhagen Study Group for Liver Diseases (1986b) 1986	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Marin (Marin et al. 1993b) 1993	Yes	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	No
Hall (Hall Larbre Spector	Yes	NR	No	Yes	NR	NR	Yes	No	No	NR	No
Sih (Sih et al. 1997b) 1997	Yes	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	No
English (English Steeds Jones	Yes	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	No
Snyder (Snyder et al. 2001b)	Yes	Yes	No	Yes	NR	Yes	Yes	Yes	No	NR	Yes
Amory (Amory et al. 2004b)	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NR	No
Kenny (Kenny Fabregas Song	Yes	NR	No	Yes	NR	NR	Yes	No	No	NR	No
Svartberg (Svartberg Aasebo	Yes	Yes	Yes	No	NR	NR	Yes	No	No	NR	No
Brockenbrough (Brockenbrough	Yes	Yes	No	Yes	NR	Yes	Yes	No	Yes	NR	Yes
Malkin (Malkin et al. 2006b)	Yes	Yes	Yes	Yes	NR	NR	Yes	No	Yes	NR	Yes
Merza (Merza et al. 2006b)	Yes	NR	Yes	Yes	NR	NR	Yes	No	No	NR	No
Nair (Nair et al. 2006b) 2006	Yes	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	Yes
Emmelot-Vonk (Emmelot-Vonk	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Svartberg (Svartberg et al.	Yes	NR	Yes	Yes	NR	Yes	Yes	No	No	NR	No
Caminiti (Caminiti et al. 2009b)	Yes	NR	Yes	Yes	NR	NR	Yes	No	No	NR	No
Chapman (Chapman et al.	yes	NR	yes	yes	NR	NR	yes	No	no	NR	No
Legros (Legros et al. 2009b)	yes	NR	yes	yes	NR	NR	yes	no	no	NR	no
Aversa (Aversa et al. 2010b)	Yes	NR	Yes	Yes	NR	NR	Yes	No	No	NR	No
Basaria (Basaria et al. 2010b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Srinivas-Shankar (Srinivas-	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NR	No

Kalinchenko (Kalinchenko et al.,	yes	yes	yes	yes	NR	yes	yes	no	no	NR	no
Jones (Jones et al. 2011b) 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	No
Ho (Ho et al., 2011) 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	NR	no
Kaufman (Kaufman et al.,	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	NR	Yes
Hoyos (Hoyos et al. 2012b)	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NR	Yes
Spitzer (Spitzer et al., 2012b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes

Source: Xu et al., 2013, Additional File 3 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648456/>)

7.4 APPENDIX D: XU ET AL. ADDITIONAL FILE 4 DESCRIPTION OF CARDIOVASCULAR-RELATED EVENTS IN THE SELECTED PLACEBO-CONTROLLED RCTS.

Author and publication year	Description of events and type of event	Count			Comment	Count of	
		Serious	T	P		Men	Events
The Copenhagen Study Group for Liver Diseases (1986b) 1986	Death from bleeding esophageal varices	Y	12	5	Unclear whether thrombosis occurred in the participants who died of other cardiovascular causes, so not included as men, but included as events.	13/5	16/5
	Death from acute myocardial infarction	Y	1	0			
	Thrombosis	N	3	0			
Marin (Marin et al., 1993b) 1993	Splanchnic venous thrombosis	N	1	0	Number of subjects by study arm obtained from Marin(Marin, Oden, & Bjorntorp, 1995) 1995	1/0	
Hall (Hall et al., 1996b) 1996	Hypertension	N	0	1		0/2	
	Cerebrovascular accident	Y	0	1			
Sih (Sih et al., 1997b) 1997	uncontrolled atrial fibrillation with congestive heart failure	Y	1	0		1/1	2/1
	Stroke	Y	0	1			
English (English et al., 2000b) 2000	Myocardial infarction	Y	1	0	First two events are recorded as withdrawals, 3 rd event is given in the 'Safety' section, unclear if it is the same event as one of the withdrawals. Counted as the same event.	2/0	
	Early elective coronary angioplasty	Y	1	0			
	Myocardial infarction when awaiting coronary revascularization	Y	1	0			
Synder (Snyder et al., 2001b) 2001	Myocardial infarction	Y	2	1	All events verified against hospital records		9/5
	Coronary bypass graft surgery	Y	2	2			
	Arrhythmia	Y	3	1			
	Other vascular events	Y	2	1			
Amory (Amory et al., 2004b) 2004	Cerebral hemorrhage	Y	1	0	An additional man developed sleep apnea in the T group	1/0	
Kenny (Kenny et al., 2004b) 2004	Cerebral vascular accident	Y	0	1			
Svartberg (Svartberg et al., 2004b) 2004	Death from probable myocardial infarction	Y	0	1		0/1	
Brockenbrough (Brockenbrough et al., 2006b) 2006	Cardiac disorders involving death	Y	3	1	Cardiac disorders included 1 death from stroke in the P group and 3 cardiovascular deaths in the T group.	9/9	
	Cardiac disorders not involving death	N	4	2			
	Access thrombosis	N	2	6			
Malkin (Malkin et al., 2006b) 2006	Arrhythmia	Y	0	2	A sudden death also occurred in the P group with unclear cause	4/4	
	Stroke	Y	1	0			
	Unstable angina pectoris	Y	1	0			
	Hospitalized for exacerbation of heart failure	Y	2	2			
Merza (Merza et al., 2006b) 2006	Angina	N	0	1		0/1	
Nair (Nair et al., 2006b) 2006	Ascending aorta dilatation	N	1	2		5/5	7/6
	CAD Stent Placement	Y	0	1			
	Chest pain	N	0	1			

	Coronary Artery bypass graft	Y	1	0		
	Coronary Artery Disease	Y	2	0		
	Frequent Ventricular Ectopics	N	1	0		
	Hypotension	N	0	1		
	Phlebitis	N	1	1		
	Triple Bypass Surgery	Y	1	0		
Emmelot-Vonk (Emmelot-Vonk et al., 2008b) 2008	Cardiovascular complaints	N	8	3	Specific types of cardiovascular event not given Includes one man who withdrew from the T group because of a cardiovascular complaint before the 3 month visit, and so was not included in the analysis presented	8/3
Svartberg (Svartberg et al., 2008b) 2008	Death from cardiac arrhythmia	Y	1	0		1/0
Caminiti (Caminiti et al., 2009b) 2009	Worsening heart failure without hospital stay	N	1	1		2/1
	Worsening heart failure with hospital stay	Y	1	0		
Chapman (Chapman et al., 2009b) 2009	Death from myocardial infarction	Y	1	0	1 ischemic chest pain in P group not counted	1/1 1/1
	Hospitalisation for myocardial infarction	Y	0	1		
Legros (Legros et al., 2009b) 2009	Death from arrhythmia and hypertrophic cardiomyopathy	Y	1	0	Another man allocated to T died of cardiac arrest 3 months after the end of the study. This event was not included.	1/0
Aversa (Aversa et al., 2010b) 2010	Acute myocardial infarction	Y	0	1	Unclear when the event occurred, i.e., when placebo group were on placebo or after they were switched to T, event included	0/1
Basaria (Basaria et al., 2010b) 2010	Acute coronary syndrome and chest pain	Y	2	0	"Two men, both in the testosterone group, underwent elective vascular procedures during treatment that were not included in these analyses since they were deemed to have been related to preexisting conditions: Subject 22 underwent elective surgery to repair an aortic aneurysm, and another participant, not listed in this table, underwent prescheduled elective angioplasty and placement of a stent in his leg owing to peripheral vascular disease". These 2 events were not included.	23/5 25/5
	Syncope	N	2	1		
	Myocardial infarction	Y	2	0		
	Angioplasty and coronary artery bypass	Y	1	0		
	Peripheral edema	N	5	0		
	Ectopy on ECG	N	1	0		
	Left ventricular strain pattern during exercise testing	N	1	0		
	ST-segment depression during exercise testing	N	1	0		
	Elevated blood pressure and atrial fibrillation	N	1	0		
	Elevated blood pressure	N	2	1		
	Chest pain	N	1	0		
	Atrial fibrillation	N	2	0		
	Stroke	Y	1	0		
	Tachycardia with fatigue	N	1	0		
	Tachycardia	N	0	1		
	Death suspected myocardial infarction	Y	1	0		
	Congestive heart failure exacerbation	Y	1	0		
	Arrhythmia –ectopy noted on CG before exercise testing	Y	0	1		
	Carotid bruit and carotid-artery plaque identified on ultra-sonography	N	0	1		
Srinivas-Shankar (Srinivas-Shankar et al., 2010b) 2010	Acute myocardial infarction	Y	0	1	Events taken from the withdrawals on flowchart and serious adverse events in text.	5/2
	Died of ruptured aneurysm	Y	0	1		

	Angina	N	1	0	Most adverse events can be found among the withdrawals. One serious adverse event (heart failure) is not listed as withdrawal. One reason for withdrawal (angina) is not listed as a serious adverse event. These were counted as separate events.	
	Pulmonary embolism (given as a serious adverse event)	Y	1	0		
	Died of constrictive pericarditis	Y	1	0		
	Abdominal aneurysm (surgery)	Y	1	0		
	Heart failure (given as a serious adverse event)	Y	1	0		
Kalinchenko (Kalinchenko et al., 2010b) 2010	angina onset	N	0	1		
	died, cause myocardial infarction	Y	0	1		0/2
Ho (Ho et al., 2011) 2011	Died myocardial infarction	Y	1	1	1 chest pain in each group not counted	1/1
Jones (Jones et al., 2011b) 2011	Died of myocardial infarction	Y	0	1	No actual numbers given, but inferred from the p-value. No information on type of event given, except that one man from the placebo group died of a myocardial infarction	5/12
	No details given	N	5	11		
Kaufman (Kaufman et al., 2011b) 2011	Myocardial infarction	Y	1	0	Of these 11 events 6 described as hypertension, but 19 cardiovascular-related events given elsewhere in the text without giving study arm	11/0
	Other vascular events	N	10	0		
Hoyos (Hoyos et al., 2012b) 2012	Cardiovascular events	N	1	0	Cardiac	1/0
Spitzer (Spitzer et al., 2012b) 2012	Cardiovascular involving hospitalization	Y	1	0	Specific types of cardiovascular event not given	4/2
	Cardiovascular not involving hospitalization	N	3	2		

Source: Xu et al., 2013, Additional File 2 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648456/>)

III. Memorandum - Office of Surveillance and Epidemiology, Division of Epidemiology II

c. Drug Use Review

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Use Review**

Date: August 20th 2014

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Office of Surveillance and Epidemiology

Subject: Testosterone and cardiovascular risk

Drug Name(s): Multiple

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2014-2704

****This document contains proprietary drug use data obtained by FDA under contract.
The drug use data/information in this document has been cleared for public release.****

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EXECUTIVE SUMMARY

This review provides an analysis of U.S. outpatient drug utilization trends for testosterone replacement therapy (TRT) products from years 2008 through 2013 stratified by patient age (0-39, 40-64, 65-74 and 75+), concurrent use of TRT products with cardiovascular medications, testing for testosterone levels prior to the initial TRT prescription and the duration of use of TRT products. This review will assist the Division of Bone, Reproductive and Urologic products (DBRUP) in its ongoing evaluation of TRT and the risk of adverse cardiovascular events in older men. The following are highlights discussed further in this review:

Sales distribution data

- The overall number of kilograms of active ingredient testosterone sold from manufacturers to all U.S. channels of distribution increased by 66% from 8,453 kg sold in 2009 to 14,023 kg in 2013. The largest relative increase was seen in injectable testosterone products, which had sales that more than doubled from 1,753 kg in 2009 to 4,470 kg in 2013. Topical testosterone products increased by 53% from 6,171 kg in 2009 to 9,451 kg in 2013.

Outpatient prescription & patient level data

- The number of unique patients with an outpatient prescription for a testosterone product increased 76% from approximately 1.3 million patients in 2010 to 2.3 million patients in 2013.
- Men between the ages of 40-64 years accounted for the largest increase in the absolute number of patients who received a prescription for testosterone in the outpatient retail setting, from approximately 844,000 patients in 2010 to 1.5 million patients in 2013.
- In year 2013, approximately 1.3 million patients (57% of testosterone users) with an outpatient prescription claim for a testosterone product had a concurrent outpatient prescription claim for a cardiovascular medication.

Office-based physician survey data

- According to U.S. office-based physician practices survey data, “testicular hypofunction” (ICD-9 257.2) was the top diagnosis associated with the use of testosterone products in men.

Commercial health plan claims data

- Out of the total of 243,091 men identified with an initial TRT prescription claim after the index date of January 1, 2008 and who had continuous eligibility during the six months prior to the index date; 72% (175,782 patients) of patients had a procedure claim for testosterone level testing *prior* to the first TRT prescription claim.
- Over a 5-year time period from 2008 through 2013, the mean cumulative treatment duration was 187 days (± 287 days) with a median of 96 days interquartile range (34, 240 days). Therefore, TRT was cumulatively used for an average of 6 months with a median of 3 months.

1 INTRODUCTION

The Division of Bone, Reproductive and Urologic products (DBRUP) reopened a Tracked Safety Issue (TSI) on Testosterone and Cardiovascular Disorders on December 20, 2013. The reopening of this TSI was prompted by the publication of two observational cohort studies reporting an association between testosterone replacement therapy (TRT) and adverse cardiovascular events in older men.^{1,2} In view of this new evidence, DBRUP consulted the Division of Epidemiology II (DEPI II) to provide an analysis of drug use data for TRT products marketed in the United States (U.S.). These data will help DBRUP in understanding the patient population utilizing TRT in the U.S. It will also assist DBRUP in its ongoing evaluation of TRT and the risk of adverse cardiovascular events in older men. Using the available drug use databases, this review provides an analysis of:

- Outpatient retail drug utilization patterns for TRT products
- Concurrent use of TRT products and a select group of cardiovascular medications.
- The presence of a procedure claim for a testosterone level test prior to receiving an initial testosterone prescription in a sample of the commercially insured population.
- Duration of use of TRT products among a sample of the commercially insured population.

1.1 BACKGROUND

On January 31, 2014, the FDA issued a Drug Safety Communication to notify the public that it is investigating the risk of stroke, heart attack and death in men taking FDA-approved testosterone products.³ The Agency has been monitoring this risk, and was prompted to reassess this safety issue based on the recent publication of two observational cohort studies. First, *Vigen et al.* showed that testosterone therapy in a cohort of veterans with significant medical comorbidities was associated with an increased risk of mortality, MI or ischemic stroke (HR 1.29; 95% CI 1.04 to 1.58).¹ Second, *Finkle et al.* reported an increased risk of heart attack in older men without pre-existing heart disease as well as younger men with pre-existing heart disease, who filled a prescription for testosterone therapy (RR 1.36; 95% CI 1.03 to 1.81).² In support of DBRUP's assessment of the risk of adverse cardiovascular events associated with TRT

¹ Vigen R, O'Donnell CI, Baron AE et al. Association of testosterone therapy with mortality, myocardial infarction and stroke in men with low testosterone levels. JAMA. 2013;210(17):1829-1836.

² Finkle WD, Greenland S, Ridgeway GK et al. Increased Risk of Non-fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men. PLoS One. 2014;9(1)e8805:1-6

³U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA evaluation the risk of stroke, heart attack and death with FDA-approved testosterone products. Posted January 31, 2014. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts>

use, DEPI II was requested to provide an analysis of drug utilization patterns for TRT products in the U.S.

1.2 REGULATORY HISTORY

The Tracked Safety Issue was initially opened in January 2010, triggered by the early termination of the Testosterone in Older Men with Mobility Limitations (TOM) trial. The TOM trial was terminated based on the disproportionate reporting of cardiovascular adverse events observed in the testosterone treatment group compared to placebo.⁴ After review of the cardiovascular findings in the TOM trial by the Division of Cardiovascular and Renal Products (DCRP), the reviewer concluded that it is not known if the results of the TOM Trial are applicable to the population for whom testosterone is indicated. Further evaluation of key publications was conducted by DEPI, including two meta-analyses and one systematic review relevant to the risk of cardiovascular disease associated with testosterone therapy in hypogonadal men, DEPI concluded that "... despite limitations of the meta-analyses and qualitative review, the results regarding overall cardiovascular risk associated with TRT compared to placebo are consistent and do not support an association between TRT and increased risk of cardiovascular events in men."⁵

1.3 PRODUCT INFORMATION

Testosterone is the primary androgen found in the body and is synthesized in the testes, ovaries and adrenal cortex. Testosterone therapy is indicated as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Therapeutically, it is used in the management of primary hypogonadism and hypogonadotropic hypogonadism that is either congenital or acquired. There are several FDA approved testosterone products in various formulations currently available in the U.S. **Table 1** lists the FDA-approved testosterone products included in this analysis.

⁴ Basaria S, Coviello AD, Travison TG. Adverse events associated with testosterone administration. N Engl J Med.2010;363(2):109-122

⁵ Alpert M and Gassman A. Memorandum: Change in Status of Safety Application Division of Reproductive and Urologic Products. Safety Application Number 865.DARRTS date January 3 2011

Table 1: FDA Approved Testosterone^{1, 2} Products

Trade Name	Initial U.S. Approval	Dosage Form
Topical products		
Androderm	9/29/1995	Patch
Androgel ³	2/28/2000	Gel
Axiron	12/1/2010	Solution
First Testosterone 2%	5/1/2001	Ointment
First Testosterone MC 2%	1/1/2003	Cream
Fortesta	12/29/2010	Gel
Testim 1%	10/31/2001	Gel
Injectable/Intramuscular products⁴		
Delatestryl	12/24/1953	Injectable
Depo-testosterone	7/25/1979	Injectable
Buccal/Oral products		
Android-10	2/9/1981	Tablet
Methitest	10/17/1974	Tablet
Striant	6/19/2003	Tablet
Testred	12/3/1973	(Extended Release) Capsule
Implants		
Testopel	7/13/1972	Pellet

¹ Analysis includes FDA approved testosterone and methyltestosterone products that showed sales activity during our study period. FDA approved testosterone/estradiol and methyltestosterone/estradiol products were not included in this analysis.

² Information obtained from Drugs@FDA. Available at <http://www.accessdata.fda.gov/scripts/cder/drugsatFDA>

³ Includes Androgel 1% and 1.62%

⁴ Analysis includes various other generic injectable and intramuscular testosterone cypionate and testosterone enanthate products not listed in Table 1

1.4 ADDITIONAL PRODUCTS INCLUDED

An analysis of the concurrent use of testosterone products (*Table 1*) with selected cardiovascular medications was conducted as a surrogate of testosterone use among patients also being treated for cardiovascular disease. The selection of the cardiovascular medications for the concurrency analysis was similar to the prescription covariates reported in the observational study conducted by *Finkle et al.*² (See *Table 9 in Appendix 2* for the list of the concurrent classes of cardiovascular medications included in this analysis).

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for testosterone products for years 2009 through

2013. Approximately 72% of testosterone bottles/packages/vials (eaches) were distributed to outpatient retail pharmacies; 22% were to mail-order/specialty pharmacies; and 6% were to non-retail settings.⁶ As a result, outpatient pharmacy utilization patterns were examined. Non-retail pharmacy data were not included in this analysis.

2.2 DATA SOURCES USED

This analysis was conducted using proprietary drug utilization databases. The time periods examined in each data source were dependent upon data availability.⁷ (See *Appendix 3* for full database descriptions)

2.2.1 Sales distribution data

The sales distribution of testosterone products, by formulation, sold from the manufacturer into various settings of distribution was measured using the IMS Health, IMS National Sales Perspectives™ database. The data obtained represent a national estimate of the number of kilograms (KG) of testosterone sold in the U.S. from 2009 through 2013. We used KG as the unit of measure to establish consistency in our analysis across time as testosterone products are supplied in a variety of formulations and packages.

2.2.2 Outpatient patient level data

The Symphony Health Solutions' Anonymous Patient Longitudinal[®] database was used to obtain the nationally projected number of unique patients with a prescription for a testosterone product in the outpatient retail setting. Given that the majority of injectable testosterone products are distributed to the retail setting, we excluded mail order facilities and clinic settings from our analysis. The patient data were stratified by patient age (0-39, 40-64, 65-74, 75+), sex, and formulation from years 2010 through 2013.

2.2.3 Office-based physician survey data

Encuity Treatment Answers™, a U.S. office-based physician survey database, was used to analyze the top diagnoses associated with the use of TRT, by patient sex and age (0-39, 40-64, 65-74 and 75+ years), for years 2009 through 2013. Utilization of testosterone products was also analyzed by concomitant diagnoses.

2.2.4 Outpatient concurrency analysis

The Symphony Health Solutions' Anonymous Patient Longitudinal[®] Concurrent Product Analyzer (SHSCPA) database provided a national estimate of the number of patients with an outpatient prescription claim for a testosterone product *concurrent* with a prescription claim for a cardiovascular medication. Prescription claims were searched using the

⁶ IMS Health, IMS National Sales Perspectives™. Year 2014. Extracted April 2014. File: TSP 865 testosterone sales in KG May 21, 2014.xls

⁷ For example, years 2009-2013 were available in IMS Health, IMS National Sales Perspectives™ and years 2010-2013 were available in the Symphony Health Solutions' Anonymous Patient Longitudinal[®] database

National Drug Codes (NDC) for testosterone products and the selected concurrent products (cardiovascular medications) from U.S. outpatient retail settings for years 2010 through 2013. Given that the majority of injectable testosterone products are distributed to outpatient retail settings we did not include Healthcare Common Procedure Coding System (HCPCS) codes to capture the administration of injectable testosterone products. A look back period of 90 days prior to the start of the study was applied to check for prescription claims within the study market to determine patient activity, since enrollment data are not available. Concurrent drug utilization data for testosterone and cardiovascular medications were stratified by patient age (0-39, 40-64, 64-74, 75+ years old).

An episode of concurrency was identified when a prescription in the *base group* (testosterone products) overlapped with the days' supply for a dispensed prescription in the *concurrent group* (cardiovascular medications). Patients with overlapping therapy days from both the *base group* and the *concurrent group* were identified as concurrent patients or patients on concurrent therapy. Therapy days were calculated by adding the number of days' supply to the date of prescription dispensing. The number of days' supply is estimated by the dispensing pharmacist based on the quantity dispensed and the specific instructions for use of the product as indicated on the prescription by the prescriber.

A grace period was applied to prescription claims to allow for days' supply time window to adjust for delays in prescription filling. We applied a conservative definition for concurrency by adding 50% to total days of supply time window in either the base group or the concurrent group. For example, if the total days of supply for a claim was 30 days, a 50% grace period would add 15 more days allowing for 45 estimated days of therapy.

2.2.5 Testing for testosterone level and duration of use

Due to limitations with the SHS data, the IMS Lifelink™ Health Plan Claims Database was used to determine whether a testosterone level test was conducted prior to a patient receiving the first testosterone prescription and/or procedure claim in a sample of the commercially insured population. The IMS Lifelink™ Health Plan Claims Database is a commercially insured health care claims database with a subset of Medicare and Medicaid patients who are enrolled in commercially administered plans. To conduct this analysis, we extracted all prescription and medical claims for male patients with a prescription and/or procedure claim for any testosterone replacement therapy (TRT) from 2007 through 2013. TRT claims included prescriptions received through pharmacies and injections administered in a physician office and billed using HCPCS codes. A complete listing of the HCPCS codes is provided in **Table 10 in Appendix 2**. The products included in the analysis are listed in **Table 1**.

The analysis included all incident users of TRT who received their first prescription or administration (the index TRT) after January 1, 2008. Incident users were defined as patients with continuous eligibility for 6 months *prior* to the index TRT date and no testosterone product prescription and/or procedure claim in the 6 months prior to the index TRT claim. Lab testing was identified using the current procedural terminology (CPT) codes listed in **Table 11 in Appendix 2**. Time between lab testing and the first administration was calculated as the number of days elapsed between the most current lab

test *prior* to the index TRT claim. For patients without testing prior to the index TRT, we calculated the number of days to the first lab test *after* the index TRT.

To determine the duration of use of TRT, we created *treatment episodes* of TRT by linking subsequent TRT claims using the days' supply obtained from the prescription claim. For TRT administered by providers, the intended days' supply field is not provided on the claim. We therefore assigned a days' supply based on the individual patient's median time between TRT administration claims. The days' supply for patients with only one HCPCS code billed administration was assigned as the median days' supply for the entire cohort. To account for patient behavior and short gaps between subsequent prescriptions, we allowed a grace period of 25% of the days' supply of the last prescription.

We provide descriptive summary statistics for the per-patient number of prescriptions, number of episodes, episode length, and cumulative duration of treatment. Note that these data are not nationally projected.

3 RESULTS

3.1 SALES DISTRIBUTION DATA

Table 2 and **Figure 1** in **Appendix 1** provide the nationally estimated number of kilograms of testosterone products sold from the manufacturer to all U.S. channels of distribution from 2009 through 2013. There was a total of 59,001 kg of testosterone products sold from 2009 through 2013. By formulation, topical testosterone products accounted for the largest proportion of testosterone products sold during the examined time, accounting for approximately 71% (41,767 kg) of sales. Injectable testosterone products were the second largest proportion, accounting for approximately 24% (14,206 kg) of sales. Buccal and oral products accounted only for 0.2% of total testosterone sales, while other formulations such as implants accounted for approximately 5% of total testosterone product sales. The proportions of sales by formulation were similar across the examined time period.

The overall number of kilograms sold of the active ingredient testosterone increased by 66% from 8,453 kg in 2009 to 14,023 kg in 2013. The largest relative increase was seen in injectable testosterone; sales more than doubled from 1,753 kg in 2009 to 4,470 kg in 2013. Topical testosterone products followed with a 53% increase from 6,171 kg in 2009 to 9,451 kg in 2013. Conversely, the sales in kilograms of buccal/oral testosterone products and other formulations such as implants declined across the examined time period.

3.2 OUTPATIENT PATIENT LEVEL DATA

Table 3 and **Figures 2 and 3** in **Appendix 1** provide the nationally estimated number of unique patients with a prescription claim for TRT stratified by patient sex, age, and formulation. In year 2013, approximately 2.3 million patients had a prescription claim for TRT from an outpatient retail pharmacy. Among those patients, men accounted for 97% (2.2 million patients) and women accounted for 3% (58,500 patients). Men 40-64 years old accounted for the largest portion (69% or 1.5 million patients), followed by men aged

65-74 years old (14% or 301,500 patients). Men between the ages 0-39 accounted for 13% (298,000) of patients in 2013, followed by men 75+ years old at 4% (87,000).

The number of unique patients with an outpatient retail prescription claim for a testosterone product increased 76% from approximately 1.3 million patients in year 2010 to 2.3 million patients in year 2013. Among men, testosterone users increased 83% from 1.2 million patients in 2010 to 2.2 million patients in 2013. Men between the ages 40-64 years accounted for the largest increase in the absolute number of patients from approximately 844,000 patients in 2010 to 1.5 million patients in 2013, a 78% increase. The number of patients between the ages 0-39 years doubled (150,000 patients in 2010 to 298,000 patients in 2013) while patients aged 65-74 increased by 65% (183,000 patients in 2010 to 301,500 in 2013) during the same examined time.

Among men between the ages 40-64 years of age, which showed the largest increase in the absolute number of patients exposed to TRT, the largest increase occurred in exposure to injectable TRT products (275,000 patients in 2010 to 633,000 in 2013; +130%), followed by topical TRT products (597,000 patients to 976,000 patients; +64%). The exposure to buccal/oral products and other formulations such as implants declined during the examined time period.

3.3 OFFICE-BASED PHYSICIAN SURVEY DATA

Table 4 in *Appendix 1* displays the top and concomitant diagnoses by ICD-9 code associated with drug uses⁸ of testosterone products by men, stratified by age, for years 2009 through 2013, cumulative. According to U.S. office-based physician practices survey data, “testicular hypofunction” (ICD-9 257.2) was the top diagnosis associated with the use of testosterone products in men 0-39 years (85% of drug use mentions), 40-64 years (91% of drug use mentions), 65-74 years (91% of drug use mentions) and 75+ years (86% drug use mentions). For testosterone product use associated with the diagnosis of “Testicular Hypofunction”, the diagnosis of “Hypertension NOS” (ICD-9 401.9) was the top concomitant diagnosis in men 0-39 years (10% of drug use mentions), 40-64 years (17% of drug use mentions) and 65-74 (19% of drug use mentions). In patients 75+ years old, the diagnosis of “Hypertension NOS” was the second (12% of drug use mentions) most common concomitant diagnosis associated with testosterone products when mentioned in association with testicular hypofunction. Overall, prescribing trends appear to be similar across the age groups with testicular hypofunction being the most common diagnosis associated with the use of testosterone products and hypertension the most common *concomitant* diagnosis among these patients.

3.4 OUTPATIENT CONCURRENCY ANALYSIS

⁸ The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 5 in **Appendix 1** provides the nationally estimated numbers of patients with a prescription claim for a testosterone product and a concurrent prescription for a cardiovascular medication from U.S. outpatient retail pharmacies, by patient age, from year 2010 through 2013. In year 2013, approximately 1.3 million patients (57% of testosterone patients) with a claim for a testosterone product had a concurrent claim for a cardiovascular medication. This is an increase in the number of patients from 738,000 concurrent patients (57% of testosterone patients) in 2010. However, the proportion of patients with a claim for testosterone product concurrently with a cardiovascular medication remained steady (approximately 57% of testosterone patients) throughout the examined time period.

Utilization by age in year 2013, showed that patients between the ages 40-64 years old had the largest *number* of patients (approximately 942,000 patients; 59.5% of testosterone patients) on testosterone with a concurrent prescription for a cardiovascular medication. However, patients in the age group 65-74 years old had the largest *proportion* of patients (218,000 patients; 71% of testosterone patients) with a claim for testosterone product and a cardiovascular medication in year 2013. Overall, the *number* of patients with a prescription claim for a testosterone product and a concurrent cardiovascular medication increased across all age groups during the examined time.

3.5 TESTING FOR TESTOSTERONE LEVEL AND DURATION OF USE

Using the IMS Life Link™ Health plan claims database, a total of 243,091 men were identified with an initial TRT prescription and/or procedure claim after the index date of January 1, 2008 and had 6 month eligibility prior to the index date. Patient characteristics of the study population are shown in **Table 6 in Appendix 1**. Approximately 73% of the TRT users in our study population were aged 40-64 years (177,764 patients); 15% (35,406 patients) were between the ages 0-39 years; 9% (23,024 patients) were between the ages 65-74 and 3% (6,867 patients) of the patients were 75 years or older during the study period.

Out of the total of 243,091 men identified with an initial TRT prescription and/or procedure claim, after the index date of January 1, 2008, 175,782 patients (72%) had a procedure claim for testosterone level testing *prior* to the first TRT prescription claim. The median number of days between a claim for a testosterone lab test and the initial TRT claim among this cohort was 36 days (interquartile range 11, 241 days). Out of the total of 243,091 patients in our sample, 15,653 patients (6% of total patients) had a claim for testosterone level testing *after* the initial TRT claim. The median number of days between a TRT claim and the first testing for a testosterone level among these patients was 166 days (interquartile range 66, 400 days). The remaining 51,656 patients (21%) did not have a claim for testosterone level testing captured during the time period used for this analysis. (*See Table 7 in Appendix 1*)

In the duration of use analysis, we used the same sample of 243,091 patients that met our initial inclusion criteria of having the initial TRT prescription and/or procedure claim after the index date of January 1, 2008 and who had continuous eligibility 6 months prior to the index date. The mean (\pm SD) number of prescriptions dispensed per patient during

the cumulative five year time period was 7 (± 10) prescriptions with a median of 2 (interquartile range 2, 9 prescriptions). The mean (\pm SD) number of *treatment episodes*⁹ per patient was 4 (± 5) episodes with a median of 2 (interquartile range 1, 5 episodes). The mean duration of an episode per patient was 47 (± 65) days with a median of 30 days (interquartile range 14, 50 days). Over the 5 year time period, the mean cumulative treatment duration was 187 (± 287) days with a median of 96 (interquartile range 34, 240 days). Therefore, TRT was cumulatively used for an average of 6 months with a median of 3 months overall. (See *Table 8 in Appendix 1*)

4 DISCUSSION

The purpose of this review is to characterize the patient population using TRT in the U.S. Our findings show that testosterone sales increased between 2009 through 2013. Topical testosterone products accounted for the largest proportion of sales across the cumulative time period; however, the sales of injectable testosterone products accounted for the largest relative increase in sales across the cumulative time period. Similar to our sales data analysis, the number of unique patients exposed to TRT increased across the examined time period. Our analysis showed that TRT is predominantly used by middle aged men between 40-64 years of age. The patient utilization of topical testosterone products dominated the market followed by injectable products. However, the largest relative increase in the number of patients exposed to TRT was seen in injectable products.

Across all the age groups examined, the largest proportions of TRT drug use mentions were associated with the diagnosis of “Testicular hypofunction NEC”. For a majority of men between the ages of 0-39 years and 40-64 years “Testicular hypofunction NEC” was the only diagnosis associated with TRT drug use mentions. The non-specificity of this hypogonadal diagnosis coupled with the nearly two-fold increase in use of TRT among men between the ages of 0-39 and 40-64 years make it unclear what criteria clinicians may be using for prescribing TRT. This increase in TRT use may also be due in part to the direct to consumer advertising encouraging testosterone use for non-specific symptoms such as decreased energy and sexual interest.¹⁰

When examining other concomitant diagnoses captured in patients associated with the use of TRT, hypertension was the most common concomitant diagnosis among the other concomitant diagnoses across most age groups. This indicates that a proportion of patients using TRT may also suffer from cardiovascular diseases such as hypertension. This finding was corroborated by our concurrency analysis which showed a large proportion of patients with a prescription claim for TRT also had a concurrent prescription claim for at least one other cardiovascular medication across most age groups.

⁹ *Treatment episode* for TRT was defined by linking subsequent TRT claims using the days supply obtained from the prescription claim. To account for patient behavior and short gaps between subsequent prescriptions, we allowed a grace period of 25% of the days supply of the last prescription.

¹⁰ Schwartz LM, Woloshin S. Low “T” as in “template” How to sell disease. JAMA Intern Med. 2013 Aug; 173(15):1460-2

In our study population of commercially insured patients, testing for testosterone level *before* the initiation of the first TRT prescription occurred in 72% of men included in our study sample. Furthermore, 6 % of our total sample population had a testosterone level test only *after* the initiation of the first TRT prescription. Approximately 21% of the study patients did not have a claim for a testosterone level test captured. These findings are consistent with another study conducted using U.S. claims data from 2001-2011 which found 74.7% of patients had undergone testing for testosterone levels. However, both our analysis and the findings of this study give no information about the proportion of these patients that actually have low testosterone levels.¹¹

We found that over a 5 year study period from years 2008 through 2013, the duration of TRT use was generally short, around an average of 6 months with a median of 3 months, and a mean of 4 episodes per patient. These results are consistent with the finding of at least one other study. A study based on U.S. claims data from 2009-2010 found an average length of therapy for topical testosterone to be approximately 4 to 5 months among hypogonadal men.¹² Although the optimal duration of therapy for TRT in hypogonadal men is unknown, a review of the literature showed that improvements in symptoms such as sexual interest, quality of life and lipid profile may occur as early as 3 to 4 weeks. Changes in symptoms such as erections and body morphology take longer ranging from 3 to 6 months, and in some cases up to 1 year.¹³

Findings from this review should be interpreted in the context of the known limitations of the databases used. The sales distribution data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into all the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. Using the sales distribution data, we estimated that testosterone products were distributed primarily to the outpatient retail pharmacy setting. We focused our analysis only on the outpatient retail pharmacy settings, therefore the patient exposure estimates reported in this review may not apply to other settings of care in which these products are used (e.g. mail-order and clinics).

Indications for use were obtained using a monthly survey of 3,200 office-based physicians representing 30 specialties across the United States who report on all patient activity during one typical workday a month. These data are helpful to understand how physicians prescribe drug products; however, the small sample size associated with the concomitant diagnosis associated with the use of TRT may limit our ability to identify trends in the data. In general, physician survey data are most appropriate to identify the typical uses for a product in clinical practice. Results should not be overstated when

¹¹ Baillargeon J, Urban RJ, Ottenbacher KJ et al. Trends in Androgen Prescribing in the United States, 2001 to 2011. JAMA intern Med.2013 Aug;173(15):1465-1466

¹² Schoenfeld MJ, Shortridge E, Zhanglin C. Medication adherence and treatment patterns for hypogonadal patients treated with topical Testosterone therapy: A retrospective medical claims analysis. J Sex Med 2013;10:1401-1409.

¹³ Saad J, Aversa A, Isidori A et al. Onset of effects of testosterone treatments and time span until maximum effects are achieved. Eur J Endocrinol 2011;165:675-85

nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

When examining concurrency, several assumptions are made: (1) a patient is actually taking the prescription(s) as recommended; and (2) the days' supply for a prescription is recorded to accurately reflect how the patient is actually taking the prescription. Mail-order pharmacies typically dispense chronic use medications such as antihypertensive and diabetic medications in large quantities more often than retail pharmacies. The SHSCPA analysis did not capture data from mail-order pharmacies. Thus, our concurrency analysis only explored patient exposure in the outpatient retail pharmacy setting, excluding mail order and non-retail settings. The impact of this limitation would be that our analysis may underestimate the true prevalence of patients on a testosterone prescription and a concurrent cardiovascular medication.

There are also some limitations to our duration of use analysis and testosterone testing analysis. First, the duration of use was determined based on days' supply of prescription dispensing in a commercially insured sample population. Therefore, prescriptions or tests paid for out of pocket or through other types of insurers would not be included in the analysis. Moreover, we do not know if the patients actually used the medication or whether the dispensing pharmacists accurately estimated the days' supply. In this situation, the actual treatment duration may be longer than our estimates. Second, we did not exclude any patients with zero or more than 100 days of supply which may have skewed our results. Third, the duration of use and testing for testosterone level analysis was limited by the observation period and presence of the patients in the database; as such the cumulative duration of use, the lifetime number of episodes, and claims for testosterone testing could have been underestimated. Lastly, The IMS Lifelink Health Plan Claims database used for the duration of use and testing for testosterone level analysis were obtained from a sample of healthcare claims representing a commercially insured U.S. population, with a subset of managed Medicare and Medicaid patients; therefore it represents only this sample and is not nationally projected. Patients aged 65 years and older might be underestimated because we likely do not have all of their claims due to Medicare switching in this population.

5 CONCLUSION

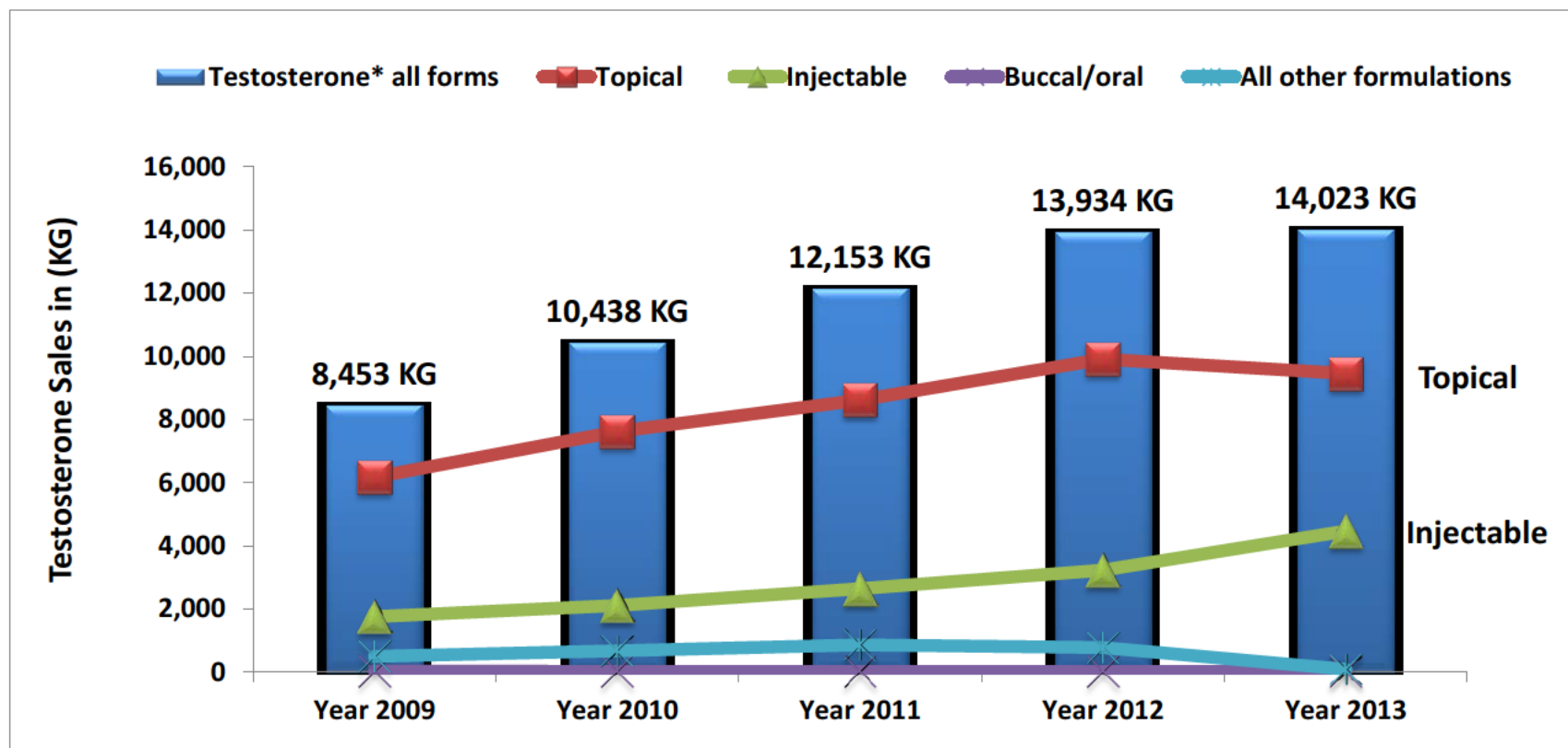
The analysis showed that prescriptions of TRT received by patients increased between 2009 through 2013. The TRT market in the most recent years was dominated by topical products followed by injectable products while all other formulations played a minor role. Users for TRT therapy were predominantly men between the ages 40 to 64 years. The most common diagnosis associated with the use of TRT was the non-specific diagnosis of "Testicular hypofunction". Our concurrency analysis revealed that a majority of TRT users, particularly older patients, concomitantly had a prescription for at least one cardiovascular medication. The duration of use of TRT was generally short, with an average of 6 months and a median of 3 months per patient during our five year study period. Testing for testosterone levels was conducted prior to the initial TRT prescription in about three-fourths of our study sample.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Figure 1

Nationally estimated number of kilograms (KG) of testosterone sold from manufacturers to U.S. channels of distribution, by formulation, years 2009 through 2013



*Includes methyltestosterone products

Source: IMS Health National Sales Perspectives™ Jan 2009 to Dec 2013. Extracted May 21/2014. File: NSP TSI 865 Testosterone Sales in KG

Table 2

Nationally estimated number of kilograms (KG) of testosterone sold from manufacturers to all U.S. channels of distribution, stratified by formulation, years 2009 through 2013

	Year 2009		Year 2010		Year 2011		Year 2012		Year 2013		Y2009-2013	
	KG	Share(%)	KG	Share (%)	KG	Share (%)	KG	Share (%)	KG	Share (%)	Total KG	Share(%)
Testosterone* all forms (KG)	8,453	100%	10,438	100.0%	12,153	100%	13,934	100%	14,023	100%	59,001	100.0%
Topical	6,171	73.0%	7,620	73.0%	8,616	70.9%	9,909	71.1%	9,451	67.4%	41,767	70.8%
Retail	4,555	73.8%	5,624	73.8%	6,431	74.6%	7,786	78.6%	7,478	79.1%	31,873	76.3%
Non-Retail	274	4.4%	321	4.2%	379	4.4%	445	4.5%	453	4.8%	1,872	4.5%
Mail-order	1,343	21.8%	1,675	22.0%	1,807	21.0%	1,678	16.9%	1,520	16.1%	8,022	19.2%
Injectable	1,753	20.7%	2,112	20.2%	2,643	21.7%	3,228	23.2%	4,470	31.9%	14,206	24.1%
Retail	1,076	61.4%	1,296	61.4%	1,661	62.8%	2,155	66.7%	3,134	70.1%	9,322	65.6%
Non-Retail	518	29.6%	609	28.8%	729	27.6%	891	27.6%	1,156	25.9%	3,903	27.5%
Mail-order	159	9.1%	207	9.8%	253	9.6%	182	5.6%	180	4.0%	981	6.9%
Buccal/Orals	32	0.4%	28	0.3%	26	0.2%	22	0.2%	17	0.1%	125	0.2%
Retail	24	73.5%	20	70.7%	18	68.3%	16	73.4%	12	72.7%	90	71.6%
Non-Retail	2	5.5%	2	6.0%	2	5.9%	1	5.4%	1	5.9%	7	5.8%
Mail-order	7	21.0%	7	23.3%	6	23.1%	5	21.2%	4	21.4%	28	22.0%
All other formulations**	496	5.9%	678	6.5%	868	7.1%	775	5.6%	86	0.6%	2,903	4.9%
Retail	354	71.3%	469	69.1%	568	65.4%	469	60.6%	79	91.9%	1,938	66.8%
Non-Retail	117	23.7%	197	29.1%	253	29.2%	244	31.5%	4	4.6%	816	28.1%
Mail-order	25	5.1%	12	1.8%	47	5.4%	62	8.0%	3	3.5%	149	7.7%

* Includes methyltestosterone products

** Includes implant and powder formulations

Source: IMS health National Sales Perspectives™ Jan 2009 to Dec 2013. Extracted May 21 2014. File: NSP TSI 865 Testosterone Sales in KG.xls

Table 3

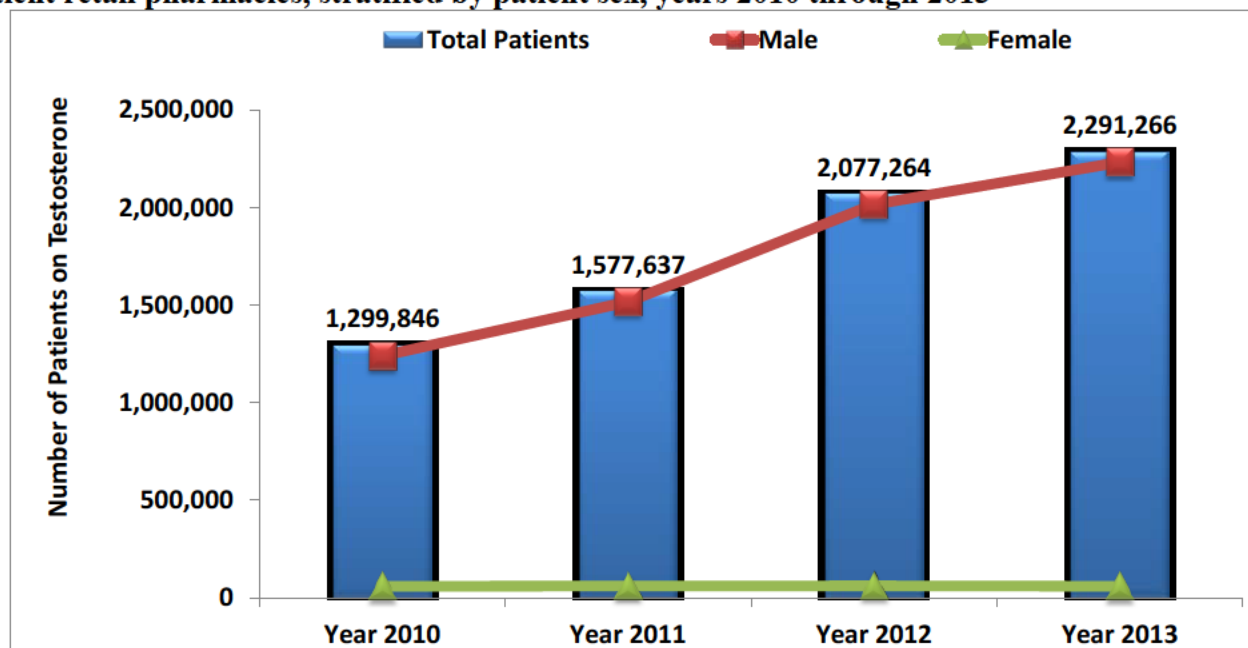
Nationally estimated number of patients with a prescription claim for a testosterone product from U.S. outpatient retail pharmacies, stratified by patient sex, age (0-39, 40-64, 65-74, 75+), and formulation, years 2010 through 2013

	Year 2010		Year 2011		Year 2012		Year 2013	
	Patient Count (N)	Share	Patient Count (N)	Share	Patient Count (N)	Share	Patient Count (N)	Share
Testosterone Total	1,299,846 (%)	100.0%	1,577,637 (%)	100%	2,077,264 (%)	100.0%	2,291,266 (%)	100%
Male	1,240,742	95.5%	1,517,712	96.2%	2,016,118	97.1%	2,232,783	97.4%
0-39 years	149,767	12.1%	191,993	12.7%	258,858	12.8%	298,408	13.4%
Topical forms	88,047	58.8%	108,287	56.4%	140,848	54.4%	142,457	47.7%
Injectable forms	69,498	46.4%	94,493	49.2%	132,527	51.2%	172,547	57.8%
Buccal/Oral forms	1,011	0.7%	857	0.4%	802	0.3%	685	0.2%
All Other forms	287	0.2%	456	0.2%	490	0.2%	36	<0.1%
40-64 years	843,876	68.0%	1,040,735	68.6%	1,391,803	69.0%	1,545,929	69.2%
Topical forms	597,054	70.8%	723,083	69.5%	949,291	68.2%	976,708	63.2%
Injectable forms	275,133	32.6%	356,754	34.3%	498,381	35.8%	633,148	41.0%
Buccal/Oral forms	6,191	0.7%	5,542	0.5%	4,946	0.4%	3,541	0.2%
All Other forms	2,651	0.3%	2,496	0.2%	2,234	0.2%	525	<0.1%
65-74 years	183,069	14.8%	213,871	14.1%	279,678	13.9%	301,575	13.5%
Topical Forms	124,023	67.7%	142,744	66.7%	185,009	66.2%	187,884	62.3%
Injectable Forms	63,540	34.7%	77,244	36.1%	103,080	36.9%	123,527	41.0%
Buccal/Oral Forms	1,296	0.7%	1,010	0.5%	769	0.3%	564	0.2%
All Other Forms	888	0.5%	564	0.3%	567	0.2%	151	0.1%
75+ years	63,988	5.2%	71,077	4.7%	85,725	4.3%	86,788	3.9%
Topical Forms	40,237	62.9%	44,284	62.3%	53,547	62.5%	51,051	58.8%
Injectable Forms	24,545	38.4%	28,166	39.6%	34,198	39.9%	37,861	43.6%
Buccal/Oral Forms	475	0.7%	344	0.5%	299	0.3%	197	0.2%
All Other Forms	494	0.8%	285	0.4%	277	0.3%	131	0.2%
Female	59,104	4.5%	59,925	3.8%	61,146	2.9%	58,483	2.6%
0-39 years	9,899	16.7%	11,175	18.6%	13,130	21.5%	15,001	25.7%
Topical forms	3,859	39.0%	3,751	33.6%	3,919	29.8%	3,629	6.2%
Injectable forms	5,051	51.0%	6,724	60.2%	8,928	68.0%	11,423	19.5%
Buccal/Oral forms	391	3.9%	291	2.6%	237	1.8%	160	0.3%
All Other forms	778	7.9%	623	5.6%	285	2.2%	67	0.1%
40-64 years	41,191	69.7%	41,500	69.3%	40,699	66.6%	36,415	62.3%
Topical forms	20,125	48.9%	21,006	50.6%	20,762	51.0%	17,554	48.2%
Injectable forms	11,099	26.9%	13,194	31.8%	15,609	38.4%	17,366	47.7%
Buccal/Oral forms	2,251	5.5%	1,706	4.1%	1,225	3.0%	998	2.7%
All Other froms	8,228	20.0%	6,036	14.5%	3,492	8.6%	879	2.4%
65-74 years	5,658	9.6%	5,256	8.8%	5,397	8.8%	5,394	9.2%
Topical Forms	2,731	48.3%	2,650	50.4%	2,864	53.1%	2,782	51.6%
Injectable Forms	1,502	26.5%	1,695	32.2%	1,977	36.6%	2,357	43.7%
Buccal/Oral Forms	332	5.9%	273	5.2%	232	4.3%	177	3.3%
All Other Forms	1,169	20.7%	703	13.4%	390	7.2%	135	2.5%
75+ years	2,357	4.0%	1,995	3.3%	1,921	3.1%	1,674	2.9%
Topical Forms	982	41.7%	929	46.6%	916	47.7%	738	44.1%
Injectable Forms	686	29.1%	616	30.9%	733	38.2%	772	46.1%
Buccal/Oral Forms	78	3.3%	86	4.3%	57	3.0%	45	2.7%
All Other Forms	644	27.3%	384	19.2%	229	11.9%	137	8.2%

Source: Symphony Healthcare Solutions Anonymous Patient Longitudinal Database® Years 2010-2013. Extracted May 2014. File Testosterone TSI #865 table & graphs.xls

Figure 2

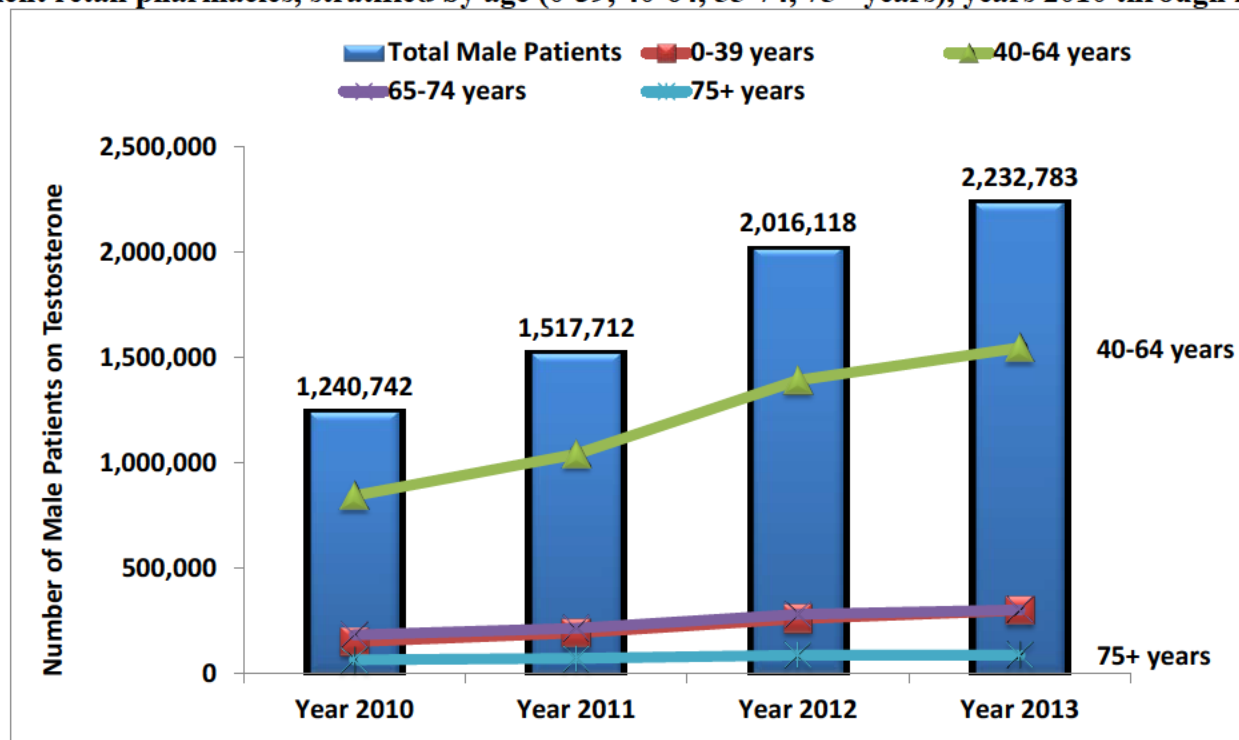
Nationally estimated number of patients with a prescription claim for a testosterone product in U.S outpatient retail pharmacies, stratified by patient sex, years 2010 through 2013



Source: Symphony Healthcare Solutions Anonymous Patient Longitudinal Database® Years 2010-2013. Extracted May 2014. File Testosterone TSI #865 table & graphs.xls

Figure 3

Nationally estimated number of men with a prescription claim for a testosterone product in U.S outpatient retail pharmacies, stratified by age (0-39, 40-64, 55-74, 75+ years), years 2010 through 2013



Source: Symphony Healthcare Solutions Anonymous Patient Longitudinal Database ® Years 2010-2013. Extracted May 2014. File Testosterone TSI #865 table & graphs.xls

Table 4

Top and concomitant diagnoses associated with testosterone products by the number of drug use mentions, stratified by patient sex and age, as reported by U.S office based physician practices, years 2009 - 2013

	Years 2009-2013 (Cumulative)			
	Uses (N)	Share (%)	95% Confidence Interval	
TESTOSTERONE PRODUCTS TOTAL USES	8,462,000	100.0%	8,019,000	8,906,000
Male Patients	6,913,000	81.7%	6,512,000	7,313,000
0-39 years	778,000	11.3%	644,000	913,000
2572 TESTICULAR HYPOFUNC NEC	664,000	85.4%	540,000	788,000
Concomitant Diagnoses				
Only Diagnosis***	391,000	58.8%	296,000	486,000
4019 HYPERTENSION NOS	66,000	9.9%	27,000	105,000
6078 OTH DISORDERS OF PENIS	46,000	6.9%	13,000	78,000
All Others	280,000	42.2%	200,000	361,000
40-64 years	4,653,000	67.3%	4,324,000	4,982,000
2572 TESTICULAR HYPOFUNC NEC	4,230,000	90.9%	3,917,000	4,544,000
Concomitant Diagnoses				
Only Diagnosis***	2,168,000	51.3%	1,944,000	2,393,000
4019 HYPERTENSION NOS	711,000	16.8%	582,000	839,000
2500 DIABETES MELLITUS UNCOMP	332,000	7.9%	244,000	4,200,000
All Others	2,567,000	60.7%	2,322,000	2,811,000
65-74 years	987,000	14.3%	835,000	1,138,000
2572 TESTICULAR HYPOFUNC NEC	896,000	90.8%	752,000	1,040,000
Concomitant Diagnoses				
Only Diagnosis***	295,000	32.9%	212,000	377,000
4019 HYPERTENSION NOS	170,000	19.0%	107,000	233,000
2500 DIABETES MELLITUS UNCOMP	136,000	15.1%	79,000	192,000
All Others	812,000	90.6%	675,000	950,000
75+ years	393,000	5.7%	297,000	488,000
2572 TESTICULAR HYPOFUNC NEC	339,000	86.2%	250,000	427,000
Concomitant Diagnoses				
Only Diagnosis***	144,000	42.6%	86,000	202,000
6000 HYPERTROPHY OF PROSTATE	56,000	16.6%	20,000	92,000
4019 HYPERTENSION NOS	41,000	12.1%	10,000	72,000
All Others	208,000	61.3%	138,000	277,000
Female Patients	848,000	10.0%	708,000	988,000

* NOS: not otherwise specified

** NEC: not elsewhere classified

***The diagnosis of "testicular hypofunction" was the only diagnosis mentioned during the visit, no other concomitant diagnoses were mentioned
Encuity Research LLC, Treatment Answers™ recommends caution interpreting projected annual uses below 100,000 as the sample size is very small with correspondingly large confidence intervals

Source: Encuity Research , LLC Treatment Answers™. Years 2009-2013. Extracted April 2014. File PDDA CP Testosterone con Dx age, gender other 4.4.14

Table 5

Nationally estimated number of patients with a prescription claim for a testosterone product and a concurrent claim for a cardiovascular medication from U.S. outpatient retail pharmacies, stratified by patient age, from years 2010 through 2013

	Year 2010			Year 2011			Year 2012			Year 2013		
	Testosterone	Concurrent*		Testosterone	Concurrent*		Testosterone	Concurrent*		Testosterone	Concurrent*	
	Patient (N)	Patient (N)	Share(%)	Patient (N)	Patient (N)	Share(%)	Patient (N)	Patient (N)	Share(%)	Patient (N)	Patient (N)	Share(%)
Testosterone Products	1,299,846	737,892	56.8%	1,577,637	903,893	57.3%	2,077,264	1,171,505	56.4%	2,291,266	1,309,063	57.1%
0-39 years	159,665	33,841	21.2%	203,167	47,714	23.5%	271,988	69,230	25.5%	313,409	88,472	28.2%
40-64 years	885,067	502,104	56.7%	1,082,235	629,885	58.2%	1,432,502	831,525	58.0%	1,582,344	941,965	59.5%
65-74 years	188,727	148,041	78.4%	219,127	169,113	77.2%	285,067	206,920	72.6%	306,969	218,203	71.1%
75+ years	66,345	53,886	81.2%	73,071	57,154	78.2%	87,645	63,788	72.8%	88,462	60,370	68.2%

Source: Symphony Health Solutions Anonymous Patient Longitudinal Database®. Years 2010-2013. File CV testosterone Concurrency_PROJ.xls

*Patients with a prescription claim for testosterone product and overlapping days supply with a prescription claim for a cardiovascular medication

Table 6

Patient characteristics of TRT users for testosterone level testing & duration of use analyses in a sample of the commercially insured population

Age at first dispensing (years)	Male Patients	Share (%)
Total number patients in study sample	243,091	100%
0-39 years	35,406	15%
40-64 years	177,764	73%
65-74 years	23,024	9%
75+ years	6,867	3%

Source: IMS Lifelink Health Plan claims Database. Reporting years 2008-2013.Extracted June 2014.

Table 7

Presence of procedure claims for testosterone level tests among male patients with a prescription and/or procedure claim for a TRT product in a sample of the commercially insured population

	Male Patients	Share (%)
Total number of patients in study sample	243,091	100%
Testosterone level testing claim prior to initial TRT prescription	175,782	72%
No claim for testosterone level testing	51,656	21%
Testosterone level testing claim present only after initial TRT prescription	15,653	6%

Source: IMS Lifelink Health Plan claims Database. Reporting years 2008-2013.Extracted June 2014.

Table 8**Duration of TRT use among a sample of commercially insured male patients**

Total number of male patients	243,091
Number of dispensing per patient (<i>prescriptions</i>)	
Mean (SD)	7(\pm 10)
Median	2
Interquartile Range	2,9
Number of treatment episodes per patient (<i>episodes</i>)	
Mean (SD)	4(\pm 5)
Median	2
Interquartile range	1,5
Mean duration of episode per patient (<i>days</i>)	
Mean (SD)	47(\pm 65)
Median	30
Interquartile range	14,50
Cumulative five year time period (<i>days</i>)	
Mean (SD)	187(\pm 287)
Median	96
Interquartile range	20,34
Source: IMS Lifelink Health Plan claims Database. Reporting years 2008-2013.Extracted June 2014.	

6.2 APPENDIX 2: ADDITIONAL INFORMATION

Table 9. Cardiovascular medications included in concurrency analysis.

Cardiovascular Medications Classes Used in Concurrency Analysis
Anticoagulants
Antiplatelets
ACE Inhibitors
Angiotensin Receptor Blockers
Antiarrhythmics
Beta-Blockers
Calcium Channel Blockers
Statins
Nitrates

Table 10. HCPCS codes used for injectable testosterone products

Drug Name	J Code
Testosterone Cypionate	J1080, J1070
Testosterone Enanthate	J3120, J3130
Testosterone Propionate	J3150
Testosterone Suspension	J3140
Testosterone Pellet	S0189

Table 11. CPT codes used for testosterone testing analysis

Test Type	CPT Code
Testosterone Free	84402
Sex Hormone Binding globulin	84270
Testosterone, total	84403

6.3 APPENDIX 3: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Symphony Health Solutions' Anonymous Patient Longitudinal Database (APLD)

The Symphony Health Solutions' Anonymous Patient Longitudinal Database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

IMS LifeLink™ Health Plan Claims Database

The IMS Health Plan Claims Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected, however, it represents approximately 9 percent of the U.S. commercially insured population based on year 2007 U.S. Census.

IV. Review of the Observational Literature for Testosterone Therapy and Cardiovascular Events –

Office of Surveillance and Epidemiology, Division of Epidemiology II and Office of Biostatistics, Division of Biometrics VII

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Date: August 12, 2014

Office of Surveillance and Epidemiology, Division of Epidemiology II

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Office of Biostatistics, Division of Biometrics VII

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Subject *Review of the observational literature for testosterone therapy and cardiovascular events*

Drug Name(s): Testosterone

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ATT	Average treatment effect for the treated
ARB	Angiotensin receptor blockers
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
cIMT	Carotid intima-media thickness
cRP	c-reactive protein
CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DBRUP	Division of Bone, Reproductive and Urologic Drugs
DB 7	Division of Biometrics 7
DEPI	Division of Epidemiology
DMII	Type II diabetes
DPV	Division of Pharmacovigilance
DSC	Drug safety communication
FAERS	FDA Adverse Event Reporting Systems
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HDL-C	High density lipoprotein cholesterol
HR	Hazard ratio
HTN	Hypertension
i.m.	Intramuscular
ITT	Intent to treat
LDL-C	Low density lipoprotein cholesterol
MI	Myocardial infarction
NDI	National Death Index
ng/dL	Nanograms per deciliter
PDE5-I	Phosphodiesterase-5 inhibitor
RCT	Randomized controlled trials
RR	Relative risk
RRR	Ratio of rate ratios
SSA	Social Security Administration
TRT	Testosterone replacement therapy
TSI	Tracked safety issue
US	United States
UK	United Kingdom
VA	Veteran's Administration
VA BIRLS	Veteran's Administration Beneficiary Identification Records Locator Subsystem

EXECUTIVE SUMMARY

This report is a joint review by the Division of Epidemiology II (DEPI) and the Division of Biometrics VII (DB7) of recently published observational studies on testosterone replacement therapy (TRT) and risk for cardiovascular events. Testosterone is an androgen steroid hormone, secreted primarily by the testicles of men and the ovaries of females, although small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid.

Testosterone containing products have been approved or used in the United States (US) since the 1950s to stimulate puberty, and for the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in men. Some formulations have also been approved for the treatment of metastatic mammary cancer in females.

In 2010, a tracked safety issue (TSI) was opened after the premature termination of the Testosterone in Older Men with Mobility Limitations (TOM) study due to an imbalance of cardiovascular-related adverse events with testosterone treatment compared to placebo. In 2011, the TSI was closed without issuance of a drug safety communication (DSC) or other regulatory actions after the FDA concluded that there was insufficient evidence to imply cardiovascular harm with TRT.

The TSI was reopened in December 2013 after the publication of the Vigen et al. 2013 study, and the Finkle et al. 2014 study was added to the TSI review after this study was published. Those studies reported an overall increased risk of cardiovascular events with TRT use compared to no therapy (Vigen) or to phosphodiesterase-5 inhibitor (PDE5-I) use (Finkle). The Finkle study also reported that certain subgroups of men, such as men over age 65 years old or younger men with heart disease, had an even higher increased risk.

As part of this review, DEPI conducted a literature search and identified three additional observational studies examining the risk of cardiovascular events with TRT; these were also included in the review (Shores et al. 2012, Muraleedharan et al. 2013, Baillargeon et al. 2014).

All five studies were retrospective cohort studies using different databases and examining a variety of cardiovascular outcomes. Two studies found statistically significant cardiovascular harm with TRT (Vigen and Finkle), two studies found statistically significant mortality benefit with TRT (Shores and Muraleedharan) and one study was inconclusive (Baillargeon).

More specifically, the Vigen study, conducted from 2005 to 2011 on male veterans post-angiography with low testosterone levels, found an increased risk of TRT compared to no TRT for a composite cardiovascular outcome (Hazard Ratio [HR] 1.29, 95% confidence interval [CI] [1.04, 1.58]). The Finkle study, conducted from 2006 to 2010 on TRT users in a large claims database, found an increased risk of non-fatal myocardial infarction (MI) when comparing the time after starting TRT to the time pre TRT (Relative risk (RR) 1.36, 95% CI [1.03, 1.81]). The Shores study, conducted from 2001 to 2005 on male veterans older than 40 years of age with low testosterone, found a decreased risk in all-cause mortality with TRT compared to no TRT (HR 0.61, 95% CI [0.42, 0.88]). The Muraleedharan study was conducted on type 2 diabetic men in the United Kingdom from 2000 to 2005. The main analysis assessed mortality in men with low serum testosterone concentration compared to men with normal serum testosterone concentration. Mortality was assessed in a subsequent subgroup analysis of treated and untreated men with low

serum testosterone concentration, and found an increased risk of all-cause mortality in men with no TRT compared to those on TRT (HR 2.30, 95% CI [1.30, 3.90]). Finally, the Baillargeon study, conducted on men older than 65 years enrolled in Medicare from 1997 to 2005, found a numerically decreased risk of hospitalization for MI for those receiving TRT compared to those without TRT (HR 0.84, 95% CI [0.69, 1.02]). The decreased risk in this last study was not statistically significant.

Due to the differences in study design characteristics and methods of analysis, the results are hard to integrate into one single summary statistic or estimate. The studies differed in databases used, patient characteristics, formulations of testosterone, follow-up times, cardiovascular outcomes, and statistical methods to adjust for confounders or time-varying covariates. Thus, none of the studies replicates the design of another study and it is unclear whether the differences in methodology, the differences in population characteristics or a play of chance led to differences in findings.

In addition, limitations within some or all of the studies included the lack of data on clinical decision making involved in prescribing TRT such as indications for TRT or disease severity. This made choosing an appropriate non-user comparator group for the TRT groups difficult and might have introduced confounding by indication. In pharmacoepidemiology, it is preferred to use a comparator group comprised of patients taking a drug or drugs treating the same disease as the test drug. However, there is no other available drug for hypogonadism. In studies using an unexposed comparator, even with the baseline characteristics collected, and using complex statistical modeling, there still could be unmeasured confounding. This highlights the need for investigators to consider alternative study designs and access to study populations with the relevant clinical data available.

Another limitation of the studies is the inability to separate the effect of TRT on cardiovascular risk from those of testosterone levels on cardiovascular risk. Serum testosterone concentrations levels over time affect both TRT dose prescribed and biomarkers of cardiovascular risk. In turn, TRT dose, adherence and effectiveness can affect testosterone levels over time. Whereas some studies had data available to correct for testosterone levels at baseline, none accounted for testosterone level over time. None of the studies could measure TRT adherence or effectiveness.

DEPI and DB7 conclude that caution should be applied when interpreting the results of these five observational studies. All five identified studies are reasonably well conducted retrospective observational studies and cardiovascular outcomes are endpoints with high positive predictive values in claims or medical records databases. However, the questions of important factors leading to TRT use and association of TRT with cardiovascular risk are hard to answer with retrospective observational studies. Because the studies used different designs and found different results, it is also hard to integrate the results.

Based on these reviewed studies, DEPI and DB7 assert that the evidence for increased risk of cardiovascular events with TRT is inconclusive. Nevertheless, while these observational studies do not provide convincing evidence for the benefit or risk associated with TRT due to the study limitations outlined; they do provide some information regarding the patient characteristics in the treated and untreated groups. Additional studies, either clinical trials or epidemiologic studies, using data sources able to capture important baseline and time varying characteristics including cardiovascular risk factors and laboratory results are needed to fully characterize the risks and benefits of TRT.

INTRODUCTION

Testosterone is an androgen steroid hormone, secreted primarily by the testicles of men and the ovaries of females, although small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In men, testosterone is key in the development of male reproductive tissues and promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair.

Some of the clinical manifestations of hypogonadism include low libido, increased body fat mass, osteoporosis and muscle wasting and weakness. Clinical guidelines recommend making the diagnosis of hypogonadism only in men with consistent signs and symptoms, and unequivocally low testosterone levels (<300 ng/dL).^{1,2} The guidelines also recommend confirmatory testing, additional work-up, and thresholds for starting and monitoring TRT (Appendix B, Figure 1).

Observational studies generally have shown that low serum testosterone concentrations are associated with the worsening of biomarkers of cardiovascular health, such as the progression of atherosclerosis,³⁻⁵ adverse lipid profile (LDL-C, total cholesterol, HDL-C)^{6,7} and high blood pressure.⁷ Some of these studies have attempted to assess clinical outcomes such as myocardial infarction⁸⁻¹⁰ and cardiovascular mortality,^{11,12} but the relationship remains unclear. RCTs have shown that testosterone therapy generally improves some of these biomarkers.¹³⁻¹⁹

However, it remains unclear whether testosterone therapy has a beneficial effect on clinical endpoints such as cardiovascular mortality, MI and stroke.

1.1 REGULATORY HISTORY

Testosterone containing products have been approved or used in the U.S. since the 1950s to stimulate puberty, and for the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in men. Some formulations have also been approved for the treatment of metastatic mammary cancer in females.

In 2010, a TSI¹ was opened in response to the premature termination of the TOM trial due to an imbalance in cardiovascular-related events in the testosterone gel group compared to placebo. The Division of Cardio-Renal Drug Products concluded that the TOM trial had important limitations that preclude a definitive assessment of the role of TRT in adverse CV outcomes and that study results might not be generalizable to the intended users of testosterone. DEPI reviewed other available data, specifically a systematic review of the literature, two meta-analyses, and the constituent studies. Neither the meta-analyses nor the systematic review provided evidence of an increased risk of cardiovascular events associated with TRT. The reviewer also noted that some of the studies demonstrated that TRT might be associated with some favorable effects on the lipid profile such as decreases in LDL or total cholesterol, but also some unfavorable effects such as a trend towards decreased HDL among TRT users (although this effect was not consistent). It is unclear whether the relatively small changes in lipid levels have

¹ A Tracked Safety Issue (TSI) refers to the tracking of activities implemented when FDA investigates significant safety issues associated with marketed drugs that require input from several FDA Divisions, Offices, another FDA Center, and/or that require a regulatory briefing, Drug Safety Oversight Board meeting, or advisory committee meeting for their evaluation

clinical relevance. DEPI concluded that based on these studies, it was not possible to conclude that TRT increases the risk of cardiovascular disease. After FDA concluded that there was insufficient evidence of cardiovascular risk with TRT, the TSI was closed without regulatory action in 2011.

The TSI was reopened in December 2013 after the publication of the Vigen *et al.* study, and the Finkle *et al.* study was added to the TSI review after it was published in January, 2014. The Vigen study reported a 1.3-fold increased risk of the composite outcome (all-cause mortality, myocardial infarction, and stroke) with TRT use compared to no use. The Finkle study showed a 1.5- to 2.2-fold increased risk for cardiovascular events with testosterone therapy in men ≥ 65 years of age, and an almost three-fold increased risk in men < 65 years with heart disease. DBRUP requested that DEPI and DB7 review these two observational studies as well as any other pertinent observational studies in the literature.

1.2 SCOPE OF DEPI AND DB7 REVIEW

DBRUP requested that DEPI and DB7 review the two observational studies (Finkle *et al.*, 2014²⁰ Vigen *et al.*, 2013²¹) as well as any other pertinent observational studies in the literature

DEPI and DB7 will provide a joint review of the Finkle *et al.*, study, Vigen *et al.*, study and other observational studies identified from a literature search.

2 METHODS AND MATERIALS

2.1 LITERATURE SEARCH

The objective of the literature search was to identify epidemiologic observational studies, safety trials and meta-analyses of RCTs assessing the association between any testosterone exposure and the outcomes myocardial infarction, stroke and mortality.

PUBMED search terms (all fields): Testosterone, cardiovascular, myocardial infarction, stroke, mortality, safety

Study restrictions

Publication dates: Last 10 years

Species: Humans only

Article types: All

The search was limited to the last ten years because the bibliographies of the recently published studies, as well as the Institute of Medicine's 2004 report 'Testosterone and Aging',²² did not list any observational studies assessing TRT and cardiovascular outcomes prior to ten years ago. In addition, an FDA librarian's search for relevant observational studies, unrestricted by year, did not yield any studies beyond the ten-year limit.

Search results: Search of the general term testosterone with combinations of the outcome search terms yielded 1,738 articles for further review.

A survey of the titles and abstracts showed that most of the articles relevant to testosterone and cardiovascular outcomes were studies or reviews of the positive or negative effects of endogenous testosterone in men. There were also reviews of the drug, editorials, pharmacology studies, preclinical studies and placebo-controlled RCTs.

Two suitable observational studies were identified from the literature search.^{23;24} Additional searches using specific testosterone brand names, the EMBASE database, and reference lists in other systematic reviews did not identify additional studies. A third suitable study was published after the literature search and is included in this review.²⁵

2.2 REVIEW MATERIALS AND METHODS

The studies reviewed in this report are:

Finkle *et al.*, 2014²⁰, Vigen *et al.*, 2013²¹, Shores *et al.*, 2012²³, Muraleedharan *et al.*, 2013²⁴, Baillargeon *et al.* 2014²⁵

A summary of each observational study and the main results are presented, followed by the DEPI and DB7 comments on the strengths and limitations.

3 REVIEW RESULTS

3.1 REVIEW OF THE FINKLE AND VIGEN STUDIES

3.1.1 Finkle Study Summary and Results

This was a retrospective cohort study conducted in a large commercial healthcare database, MarketScan (Appendix A, TABLE 1). The study evaluated whether TRT might increase the risk of acute non-fatal MI; and if the effect was more pronounced in those with pre-existing cardiac disease. Men with an initial prescription for testosterone or a PDE5-I were identified in the database. To be included in the study, they needed at least 22-months of continuous enrollment prior to TRT (N=55,593) or PDE5-I (N=167,279) initiation, be outcome-free, and have at least 90-days of follow-up time available.

The authors first used a self-control cohort method to compare the incidence rate of non-fatal MI in the 90-day period post-TRT prescription to the rate during the 12-month pre-prescription period. They found a 40% increased risk for non-fatal MI with TRT compared to the period prior to TRT initiation (RR 1.36, 95%CI [1.03, 1.81]) (Appendix A, TABLE 2). They also found men older than 65 years old had over a doubling of the risk for non-fatal MI with TRT (RR 2.19, 95%CI [1.27, 3.77]), and the risk remained the same whether or not they had a history of heart disease. In men younger than 65 years old, only those with a history of heart disease had a statistically significant increased risk for non-fatal MI in the post-prescription period compared to the pre-prescription period (RR 2.90, 95%CI [1.49, 5.62]).

In the parallel cohort analysis, the post- to pre-prescription rates of non-fatal MI in men treated with a PDE5-I were compared to the post- to pre-prescription rates with TRT using the ratio of the rate ratios (RRR) estimated from a weighted Poisson regression. Men in the TRT cohort had an observed increased risk for non-fatal MI (RRR 1.27 95% CI [0.94, 1.71]). There was an approximate doubling of the observed risk for men older than 65 years old with heart disease (RRR 1.90, 95%CI [0.66, 5.50]) and without heart disease (RRR 2.41, 95%CI [1.12, 5.17]), and for men younger than 65 years old with heart disease (RRR 2.07, 95%CI [1.05, 4.11]). No increased risk was observed in men younger than 65 years old without heart disease.

The authors concluded that in younger men with pre-existing diagnosed heart disease, and in older men, the risk of non-fatal MI following initiation of TRT is substantially increased.

3.1.2 DEPI and DB7 Comments

Of the five studies reviewed, the Finkle study had the largest sample size, and used the database MarketScan®, which covers a fairly representative US population. The study has some limitations that raise questions about whether there is a true risk for non-fatal MI with TRT.

The main advantage of the self-controlled cohort design is that it controls for measured and unmeasured (time-invariant) confounders by comparing the outcomes during treated time versus outcomes during untreated times in the same group of subjects.

However, the self-control cohort design might be more appropriate for intermittent exposures with transient outcomes. Normally, TRT is prescribed for chronic use, but in this study, follow-up was limited to 90-days post initial prescription for therapy. However, the choice of a time window of one year for the pre-TRT period and 90 days for the post-TRT period is questionable given that the treatment is for a chronic disease. In addition, this study followed patients who received an initial prescription for TRT but it is unclear whether patients actually used the TRT during the entire 90-day period. Another concern with this self-control cohort design is the potential for prescribing bias. The patients having prior MI might be less likely to receive TRT and thus the risk of MI for the pre-prescription period might be underestimated. In addition, low serum testosterone concentrations have been associated with cardiovascular risk^{13,14,15;19} and a biomarker for receiving TRT, is a critical lab result missing from the self-controlled analyses.

Using the PDE5-I drugs as an active comparator in the parallel cohort design might reduce the risk of surveillance bias, since both groups of men would have increased interactions with their physicians. However, PDE5-I therapy is mainly used for erectile dysfunction and is not indicated for hypogonadism; so, a PDE5-I is not a competing therapy and presumably not as likely to be prescribed as testosterone in hypogonadal men, and the PDE5-I drugs are used as needed compared to the chronic use of testosterone.²⁶ In addition, serum testosterone concentration data were also missing from the PDE5-I analyses.

Moreover, in the parallel cohort method, the weighting of PDE5-I treated men to match the TRT men is unclear. The authors informed FDA that the original propensity score weights were rescaled for men in the PDE5-I group with pre-prescription MI, so that the pre-prescription MI rates were numerically identical in TRT and PDE5-I groups, overall and stratified by age and history of heart disease. Although the propensity score weighting is an appropriate approach to help control for confounding, the absence of specific details about the particular rescaling in this study precludes the ability of FDA to conclude whether this approach was appropriately performed. In addition, there might still be residual confounding present, in part due to the lack of laboratory data for baseline and follow-up testosterone levels and indications for testosterone therapy.

In both the self-control and parallel cohort analyses, acute non-fatal MI was the only outcome measured, and is well validated and captured in MarketScan. Fatal MI and other outcomes such as cardiovascular mortality, or stroke were not measured. Thus, it is unclear how the inclusion of these other major cardiovascular adverse events would have affected the study results.

In this study, only the parallel cohort design informs on factors that might influence TRT use. For instance, the men prescribed TRT tended to be younger with a higher comorbidity burden compared to men in the PDE5-I cohort. For both the self-controlled cohort and the parallel cohort analyses, the overall risk was small, with a confidence

interval exactly at the null or barely excluding it. However, age and heart disease status at baseline appear to be important TRT effect modifiers.

3.1.1 Vigen Study Summary and Results

The Vigen study was a retrospective cohort study assessing the association between TRT and the composite outcome of all-cause mortality, MI and stroke among male veterans (Appendix A, TABLE 1). The cohort consisted of men who had undergone coronary angiography, and had a subsequent testosterone level less than 300 ng/dL (N=8,709). Of those, 1,223 initiated TRT and 7,486 did not initiate TRT. The average follow-up was about 840 days (540 days for the TRT group vs. 889 days for the non-TRT group). There were 123 events (67 deaths, 23 MIs, 33 strokes) for the 1,223 patients initiating TRT, and 1,587 events (681 deaths, 420 MIs, 486 strokes) for the 7,486 patients not initiating TRT. Data were collected from all the U.S. VA clinical and pharmacy databases.

Using Cox proportional hazard model with inverse probability of treatment weighting and treating TRT as a time-varying covariate, the study found a 30% increased risk for the composite outcome (HR 1.29, 95%CI [1.04-1.58]) (TABLE 2). There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, $p = 0.41$).

The authors concluded that among a cohort of male veterans who underwent coronary angiography and had low serum testosterone, the use of TRT was associated with an increased risk for adverse cardiovascular outcomes. The authors also concluded that there was no difference in the effect size of testosterone therapy among those with and without coronary artery disease.

3.1.2 DEPI and DB7 Comments

To define the cohorts, the authors chose men with low serum testosterone concentrations. However, the factors that determined which men were treated versus not treated were unknown, as information on indications for treatment was not captured in the study.

Overall, the study population had a high comorbidity burden. However, the TRT initiators tended to be younger, with lower serum testosterone concentrations and higher BMI. However, they tended to have a lower comorbidity burden compared to the non-TRT initiators.

Only 60% of the TRT cohort had testosterone levels checked after starting TRT. On average, these men had a baseline testosterone level of 176 ng/dL and post treatment level of 332 ng/dL, which is low normal. The Endocrine Society Clinical Practice guidelines recommend raising serum levels to between 400 and 700 ng/dL.¹

Most of the TRT cohort had at least one testosterone refill during the study and spent about a year on therapy. Nevertheless, despite being on therapy for about a year, the low-normal average testosterone blood levels among treated men indicates that serum testosterone concentrations did not reach therapeutic levels for at least some men. Due to these treatment uncertainties, it is difficult to attribute the increased risk for the composite outcome to TRT alone, and not consider that these men might have remained hypogonadal, which might independently affect cardiovascular risk.

The authors also found no difference in risk by the formulation of testosterone (intramuscular injections, patches, gels, pellet implants) used.

Of concern is that 128 men were excluded from the analysis due to having an MI or stroke prior to initiation of TRT. This introduced selection bias into the study and might have biased the point estimate away from the null. The authors did a post hoc analysis including these 128 men, and reported no change (HR 1.30, 95%CI [1.06, 1.60]). It is also unclear why the authors excluded 1,301 participants for not having coronary anatomy data (CAD status), considering the wealth of baseline information collected on medical and drug history. It is unclear how this exclusion might have affected the risk estimate.

The all-cause mortality variable in the composite outcome made up about half of the outcome events in each treatment group, and cause of death was not reported. Higher event rates and larger treatment effects achieved with less explicit outcome measures (such as all-cause mortality) is misleading especially when evaluating the impact of more specific outcomes, such as cardiovascular death.

The overall risk estimate was small, at 1.29. The raw composite outcome rate in the TRT cohort is half that of the untreated cohort (10.2% TRT versus 21.2% no-TRT). Yet after applying stabilized inverse probability of treatment weighting to adjust for unmeasured confounding and calculate the risk estimates, there was an increased risk for the outcome with TRT (25.7% TRT vs. 19.9% no-TRT, see Appendix A, TABLE 1). This finding was unchanged in the post hoc analysis that added potentially 128 additional outcomes to the untreated cohort.

FDA communicated with the authors regarding their statistical methods. Adjustments using inverse probability of treatment weighting were motivated by imbalances between TRT subjects, untreated subjects and also differences in TRT initiation time after coronary angiography for those treated. It is unclear how effective the weights account for selection and time of receiving treatment. A logistic regression model was fit at each event time to obtain the propensity of treatment for all patients at risk of an event at that time. The variables used in the logistic regression model to create the weights include age, race, a list of comorbidities and a list of prior cardiovascular procedures. Although no time-varying covariates were used in generating the weights, the weights were time-varying because they were calculated at each event time and men at risk varied at each event time. Lab measurements, including testosterone levels, were not used to generate the weights.

Note that in this time to event analysis, the outcome was defined as time from coronary angiography and testosterone testing to event, not time from initiating TRT to event. In addition, after a subject started TRT, they were assumed to have continued treatment until an event occurred or end of follow up. This analysis could have introduced misclassification bias for the exposure time and makes interpreting the results difficult.

After applying the weighting, the absolute risk difference between the untreated group versus the treated group, at 1-year, 2-years and 3-years after coronary angiography was found to be 1.3%, 3.1% and 5.8%, respectively. However, although the absolute risk differences appear to be increasing with time, they are modest and with increasing follow-up time, the sample sizes decreased.

3.2 REVIEW OF OTHER PUBLISHED OBSERVATIONAL STUDIES

3.2.1 Other Study Summaries and Results

Based on our literature search, we identified three additional observational studies by Shores *et al.*,²³ Muraleedharan *et al.*,²⁴ and Baillargeon *et al.*,²⁵ that assessed testosterone therapy and the risk of cardiovascular events. All three studies were done in higher risk populations. The Shores study included a veteran population with low serum testosterone levels (TRT n=398, no TRT n=633),²⁷ the Muraleedharan study included a sub-group of Type 2 diabetics with low serum testosterone concentration (TRT n=64, no TRT n=174),²⁸ and the Baillargeon study included older men in US Medicare (TRT n=6,455, no TRT n=19,065) (Appendix A, TABLE 1). While the Shores and Baillargeon studies were conducted using medical and pharmacy claims data, the Muraleedharan study collected data from medical facilities with access to medical records.

The Shores and Muraleedharan studies are fairly small but had longer follow-up than the Finkle and Vigen studies. Baillargeon's study is the second largest of the five studies reviewed. Shores uses VA data, Muraleedharan's study uses data from the UK and Baillargeon's data is from US Medicare. All three studies covered a similar time period ending in 2005.

The Shores study showed a reduction in the risk for all-cause mortality with TRT (10.3%) compared to no TRT (20.7%) (HR 0.61, 95%CI [0.42, 0.88]), and the Muraleedharan study showed a similar result with a decreased risk of death with TRT (6/64 [9%]) compared to no TRT (35/174 events [20%]) (HR 2.30, 95%CI [1.30, 3.90])². The Baillargeon study showed no risk for hospitalization due to MI for those with TRT (318 events [5.0%]) compared to those not on TRT (994 events [5.2%]) (HR 0.84, 95%CI [0.69, 1.02]). The event counts for the Baillargeon study were obtained from the author through e-mail communication (July 2014).

3.2.2 DEPI and DB7 Comments

Generally, the results from these three studies suggest that men with more comorbidities or lower baseline serum testosterone concentrations, or both might benefit from testosterone therapy.

To increase the likelihood of a symptomatic hypogonadal population, the Shores study used a lower threshold for low testosterone (<250 ng/dL) compared to the Muraleedharan study (<300 ng/dL). In both studies, lower testosterone level was associated with TRT, but increased BMI and younger age were also associated with TRT in the Shore study. In a previous study, the authors of the Shores study reviewed 300 medical records of veteran men and found that sexual dysfunction, osteoporosis and follow-up of low testosterone levels were the most common indications for measuring serum testosterone concentration.²⁹ This might give some hint at the common indications for TRT in veteran men. The Baillargeon study did not use testosterone levels to select the cohort as no lab data were available from the claims data source, but indications for TRT (fatigue, hypogonadism, osteoporosis, sexual

² This hazard ratio is expressed relative to TRT

dysfunction) and increased comorbidity load (Elixhauser score >3)³ were associated with TRT. In these three studies, these findings might indicate that testosterone was being used to treat men with lower baseline testosterone levels, or men with symptoms of hypogonadism, or both.

In addition, the Shores study showed that a lower baseline serum testosterone concentration was associated with TRT, and that testosterone treated men are at a lower risk for mortality. The Muraleedharan study showed a similar mortality rate between treated diabetic men with low baseline serum testosterone concentrations and untreated diabetic men with normal testosterone levels, which suggests that the treated men in this study are similar to the eugonadal men with respect to mortality. In the Baillargeon study, treated men at highest risk for MI at baseline (based on quartiles for MI prognostic index score) had a statistically significantly decreased risk for MI.

All three studies used a time to event analysis with some differences in implementation. The Shores study used a Cox proportional hazard model with TRT as a time-varying covariate, and adjusted for propensity scores by quintiles in sensitivity analysis. The Muraleedharan study used a Cox proportional hazard model, and adjusted baseline covariates including demographics, some biometric measurements at baseline, some comorbidities and concomitant medications. The study showed an approximate 50% reduction in the risk for death with TRT (TABLE 2).

The Baillargeon study matched TRT subjects to untreated subjects on MI prognostic risk score developed by the authors. After matching, the study used a Cox proportional hazard regression, treating TRT as a fixed covariate and adjusting for multiple baseline covariates. This study did find a trend of benefit to TRT on reducing hospitalization due to MI, but the results were not statistically significant.

From these studies, the relationship between duration of TRT and all-cause mortality or MI is unclear. The Baillargeon study was the only study to include a sensitivity analysis examining the length of treatment, but it showed no treatment difference.

While the treatment duration in each of the three studies was 1.5 years or more, the effectiveness of the therapy was unclear. Only the Muraleedharan study (over 2-years therapy) had follow-up plasma testosterone levels, which showed an average peak follow-up testosterone level of 657 ng/dL, with over 67% of the treated men with an average level over 518 ng/dL. These levels were within the recommended therapeutic range (400 – 700 ng/dL),¹ and suggest the men in that study had adequate testosterone therapy, and there was a favorable effect of therapy on all-cause mortality.

The adequacy of testosterone therapy cannot be assessed in the Shores and Baillargeon studies, as there were no follow-up tests to check post-TRT initiation serum testosterone concentrations. On average, the men in the Shores study were treated for approximately 1.5 years; while the testosterone users in the Baillargeon study had an average of 4.4 injections the first year, and 8.2 injections over the entire follow-up period. This seems infrequent given that the recommended frequency of administration was every 1-4 weeks for products available during this time. This might be indicative of poor adherence, and subsequent under treatment.

³ The Elixhauser comorbidity score is a measurement tool that defines 30 comorbid conditions using ICD-9-CM codes. It was developed using administrative data and summarizes disease burden and can discriminate for in-hospital mortality.

The potential impact of formulation on the estimate could not be assessed from these studies. The Baillargeon study only included the intramuscular testosterone formulation, the majority of the exposure in the Shores study was intramuscular testosterone, whereas the Muraleedharan study had testosterone gel as the main exposure

The outcomes measured were not consistent across the studies. Only all-cause mortality was reported as the outcome in the Shores and Muraleedharan studies, so major adverse cardiovascular outcomes that did not result in death were not captured. The Baillargeon study measured only hospitalization for MI, which might not capture men who suffered a fatal MI prior to hospitalization. None of these outcomes captured stroke and other deaths due to cardiovascular events.

4 SUMMARY COMMENTS

Indications for TRT and disease severity

From these five studies, generally it would seem that men with higher comorbidity burden, or men with lower testosterone at baseline, or both, are more likely to be prescribed TRT. However, the relationship between testosterone therapy and the outcomes were mixed.

Testosterone is used to treat hypogonadism.¹ The Vigen, Shores and Muraleedharan studies defined their cohorts by men with low testosterone levels who initiated TRT or did not initiate TRT; whereas, the Finkle and Baillargeon studies started with those who had already initiated TRT. The Muraleedharan study was conducted using medical records, and gave the most details of the decisions to initiate treatment, as well as the management of TRT. The other studies were only able to gather information on treatments, covariates and outcomes, using mainly ICD-9 diagnostic codes from VA hospital clinical databases^{27;30} or from claims databases.^{20;25}

From these data streams, common indications associated with TRT use were fatigue, hypogonadism, sexual dysfunction and osteoporosis. Generally, younger age, increased BMI and lower baseline testosterone were associated with TRT. Increased numbers of comorbidities appeared to be associated with TRT in the largest studies (Finkle and Baillargeon)^{20;25} but not in the two smallest studies (Shores, Muraleedharan).^{27;28} The Vigen study was the only one that showed a higher proportion of comorbidities in the untreated group, compared to the treated group. The higher BMI in the TRT cohort is supported by some longitudinal studies that showed an increased likelihood of having hypogonadism in obese men compared to non-obese men, which might indicate a higher likelihood for TRT.^{31;32}

Duration of TRT and therapeutic levels

Overall, the relationship between duration of TRT and the study outcomes is unclear. The Baillargeon study was the only study to include a sensitivity analysis of length of treatment, but it did not show a statistically significant decreased risk.

In the Finkle study, follow-up time was censored at 90-days post first prescription and showed a significant increase in MI. Ninety-days for the post-TRT period is questionable given that the treatment is for a chronic disease. Testosterone users in the Baillargeon had a long follow up but might have been undertreated or non-adherent due to a low number of injections in the first year and over the study follow-up period. However, this study showed no risk for MI with TRT. Neither of the studies had baseline testosterone levels available to assess disease severity, nor follow-up testosterone plasma levels to assess the effect of TRT, so the relationship between TRT and MI is unclear.

In the other three studies, the average duration of TRT use was longer. More specifically, the duration of TRT use in the Vigen, Shores and Muraleedharan studies was 10-months, 20-months and over 24-months, respectively. However, the average post-TRT testosterone level was in the sub-therapeutic range for the men in the Vigen study and in the therapeutic range for the men in the Muraleedharan study. This might indicate that under-treated or non-adherent men are at greater risk for the composite outcome (Vigen), or that men with more comorbidities, who are adequately treated have a survival advantage compared to untreated men (Muraleedharan). This would be consistent with clinical trials that have shown that TRT generally improves certain biomarkers of cardiovascular health, LDL-C, total cholesterol,⁶ insulin resistance⁶ visceral adiposity¹⁴⁻¹⁷ and cIMT,¹⁵ which might suggest a favorable effect of TRT on cardiovascular health, or visa-versa.

Outcomes

The outcomes varied across the studies, which makes an overall assessment of cardiovascular outcomes with TRT difficult. The outcomes are clinical outcomes with usually high positive predictive values in claims databases. The Shores and Muraleedharan studies only had all-cause mortality as an outcome, Vigen used a composite outcome, Finkle only used non-fatal MI, and Baillargeon used hospitalization for MI.

All-cause mortality made up about half of the outcome events in each treatment group in the Vigen study, and cause of death was not reported. Less explicit outcomes such as all-cause mortality do not provide the necessary granularity to assess what proportion of the outcome is attributable to important or relevant components, nor does it capture cardiovascular events that do not result in death. Limited outcomes such as non-fatal MI, however, could potentially miss other important major cardiovascular events.

Statistical Methods

Four of the five studies (Vigen, Shores, Muraleedharan and Baillargeon) used a time to event analysis with Cox regression. All four studies estimated HR of the different outcomes comparing TRT subjects to untreated subjects. The primary analyses were intent to treat analyses, meaning following subjects until end of follow up, not until end of treatment.

However, the definition of initial time of follow up, the TRT variable, the choice of covariates and their handling in the model varied among these four studies. Vigen, Muraleedharan and Shores used time of diagnosis of low testosterone as initial time, whereas Baillargeon used time of TRT initiation as initial time. Using time of diagnosis rather than time of initiation of therapy could lead to exposure misclassification bias.

Vigen and Shores used a time-varying TRT variable to account for differences in time from diagnosis to treatment initiation between subjects. These studies also assumed that subjects stayed on TRT after initiation. However, the Baillargeon studies used a fixed TRT variable from baseline to end of follow-up. It is unclear whether the Muraleedharan study used time varying or fixed TRT. The Baillargeon study included sensitivity analyses adjusting for time on treatment; the other studies did not explore the impact of time on treatment on the results.

Shores, Muraleedharan and Baillargeon included between 4 to 9 different variables in the Cox regression model. In addition, Baillargeon matched the cohorts on MI prognostic risk score, a composite score of more than 85 variables. In Vigen, instead of adjusting for multiple variables in the Cox regression, the study used the variables to generate

stabilized weights in inverse probability of treatment weighting correcting for possible imbalances at initiation of therapy. Although regression analysis and weighting can correct for possible imbalances in the groups, the imbalances in some studies were such that there might have been some residual confounding contributing to observed differences in risk.

The use of a self-control cohort in Finkle to estimate RR between pre-TRT and post-TRT presents many advantages since many of the potential confounders are not measurable in claims databases. The self-control design adjusts for observed and unobserved time-invariant confounders because it compares outcomes on the same subjects. However, the choice of a time window of one year for the pre-TRT period and 90 days for the post-TRT period is questionable given that the treatment is for a chronic disease. Another concern for the Finkle study is the lack of the ability to obtain laboratory values for testosterone testing, as low serum testosterone concentration is associated with cardiovascular risk.^{13;14;15-19} and is the key biomarker for receiving TRT.

All studies included different sets of covariates reflecting the demographic, comorbidities and concomitant medication information that was available in the database used. Only Shores used testosterone at baseline in the model, although that information was available in Vigen and Muraleedharan.

5 CONCLUSIONS

DEPI and DB7 conclude that caution should be applied when interpreting the results of these five observational studies.

All five studies were retrospective cohort studies with varying sample sizes. However, the study results are different, even contradictory. The Vigen (HR 1.29, 95% CI [1.04, 1.58]) and Finkle (HR 1.36, 95% CI [1.03, 1.81]) studies found a statistically significantly increased risk for a composite cardiovascular outcome and non-fatal MI, respectively. The Shores (HR 0.61, 95% CI [0.42, 0.88]) study found a statistically significant decrease in risk for all-cause mortality, and the Baillargeon study found no increased or decreased risk for MI with TRT (HR 0.84, 95% CI [0.69 - 1.02]) (Table 2). A subgroup analysis in Muraleedharan, found an increased risk of all-cause mortality of no TRT compared to TRT (HR 2.30, 95% CI [1.30, 3.90]). In all the studies, the main effect sizes were fairly small.

Due to the differences in study design characteristics and methods of analysis, the results are hard to integrate into one single summary statistic or estimate. The studies used different: databases, patient characteristics, formulations of testosterone, follow-up times, cardiovascular outcomes, and statistical methods to adjust for confounders or time varying covariates. Thus, none of the studies were able to replicate the findings of another study (Table 1).

In addition, key limitations within some or all of the studies included, lack of data on clinical decision making involved in prescribing TRT such as indications for TRT and disease severity. This made choosing an appropriate non-user comparator group for the TRT groups difficult and might have introduced confounding by indication. In pharmacoepidemiology, it is preferred to use a comparator group taking a drug or drugs treating the same disease as the test drug. However, there is no other available drug for hypogonadism. In studies using a non-exposed comparator, even with the baseline characteristics collected, and using complex statistical modeling, there still could be unmeasured confounding. This highlights the need for investigators to consider

alternative study designs and access to study populations with the relevant clinical data available.

Another key limitation of the studies is the inability to separate the effect of TRT on cardiovascular risk from those of testosterone levels on cardiovascular risk. Testosterone level over time affects both TRT dose prescribed and biomarkers associated with cardiovascular risk.^{13;14;15-19} In turn, TRT dose, adherence and effectiveness can affect testosterone levels over time. Whereas some studies could correct for testosterone levels at baseline, none could account for testosterone level over time. None of the studies could measure TRT compliance or effectiveness.

Based on these reviewed studies, DEPI and DB7 assert that the evidence for increased risk of cardiovascular events with TRT is inconclusive. But, while the reviewed observational studies do not provide convincing evidence for the cardiovascular benefit or risk associated with TRT due to the study limitations outlined; the studies do provide some information about the patient characteristics in the treated and untreated groups. Additional studies, either clinical trials or epidemiologic studies, using data sources able to capture important baseline and time varying characteristics including cardiovascular risk factors and laboratory results are needed to fully characterize the cardiovascular risks and benefits of TRT.

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7 APPENDIX A- SUMMARY OF STUDIES

Table 1 – Design Summary

Design Features	Finkle et al, 2014	Vigen et al, 2013	Shores et al, 2012	Muraleedharan et al, 2013	Baillargeon et al, 2014
Objectives/Aims/Scope	TRT and non-fatal MI in men	TRT and [all-cause mortality, MI and stroke] in men with low testosterone who underwent angiography	TRT and Mortality, in male veterans with low testosterone	TRT and mortality in men with low testosterone and type 2 diabetes	TRT and MI in older men
Data Source	Commercial claims database (MarketScan) in the US	VA clinical database in the US	VA clinical database, VA BIRLS, NDI, SSA in the US	Clinic and hospital medical records in the UK	5% national sample of Medicare in the US
Time Period	2006-2010	2005-2011	2001-2005	2000-2005	1997-2005
Criterion (Selection) Standards	Men with ≥ 22 months continuous database enrollment and 90-days post initial prescription	Male veterans post angiography, with low testosterone (<300 ng/dL)	Male veterans >40 years old with low testosterone (<250 ng/dL)	Type 2 diabetic men with low testosterone (<300 ng/dL) and at least 1 year of TRT	Men > 65 years enrolled in Medicare Part A and Part B for at least 12 months and no end-stage renal disease
Exposure/Intervention	Testosterone (gels, topicals, injections, micronized)	Testosterone (patch, gels, injections)	Testosterone	Testosterone (gels, buccal tablets, injections)	Intramuscular testosterone
Outcome(s)	Non-fatal MI (first event)	Composite: All-cause mortality, MI and stroke (first event)	Mortality	All-cause mortality	Hospitalization for MI (first event)
Comparisons of interest	(a) Self-control cohort: time pre TRT vs. time post TRT (b) TRT vs. PDE5-I	Users to non-users	Users to non-users	Users to non-users	Users of TRT to non-users

Design Features	Finkle et al, 2014	Vigen et al, 2013	Shores et al, 2012	Muraleedharan et al, 2013	Baillargeon et al, 2014
Strengths	<p>Large sample size</p> <p>Self-controlled cohort study can control for measured and unmeasured confounders</p>	<p>Large sample size</p> <p>Testosterone levels used to select the cohort</p>	<p>Testosterone levels used to select the cohort</p>	<p>Claims and medical records data</p> <p>Testosterone levels used to select the cohort</p>	<p>Large Sample Size</p> <p>Long follow up period</p> <p>Representation of all US geographic regions</p>
Limitations	<p>Testosterone levels not available in this database</p> <p>Reasons for initiating treatment unknown</p> <p>Adherence unknown</p> <p>Short follow up time</p> <p>Possible prescribing bias in self-control cohort</p> <p>Lack of comparability of TRT to PDE5-I in parallel cohort</p> <p>Unclear propensity weighting scheme in parallel cohort</p>	<p>Unknown cause of death</p> <p>Reasons for initiating treatment unknown</p> <p>Adherence unknown</p> <p>Possible selection bias due to exclusion of events pre-TRT</p> <p>Possible misclassification bias of exposure</p> <p>Time on treatment not accounted for in ITT analysis</p>	<p>Excluded more recent data</p> <p>Small sample size</p> <p>Reasons for initiating treatment unknown</p> <p>Adherence unknown</p> <p>Time on treatment not accounted for in ITT analysis</p>	<p>Excluded more recent data</p> <p>Small sample size</p> <p>Possible misclassification bias of exposure</p> <p>Time on treatment not accounted for in ITT analysis</p>	<p>Excluded more recent data</p> <p>Included only injections and not more recent formulations of testosterone</p> <p>Adherence unknown</p> <p>Could not include testosterone level (as baseline factor to define hypogonadism or risk factor for MI)</p>
<p>MI Myocardial infarction; NDI National Death Index; ng/dL Nanograms per deciliter; PDE5-I Phosphodiesterase-5 inhibitor; SSA Social Security Administration; TRT Testosterone replacement therapy; US United States; UK United Kingdom; VA Veteran's Administration VA BIRLS Veteran's Administration Beneficiary Identification Records Locator Subsystem</p>					

Table 2: Summary comparisons of study results

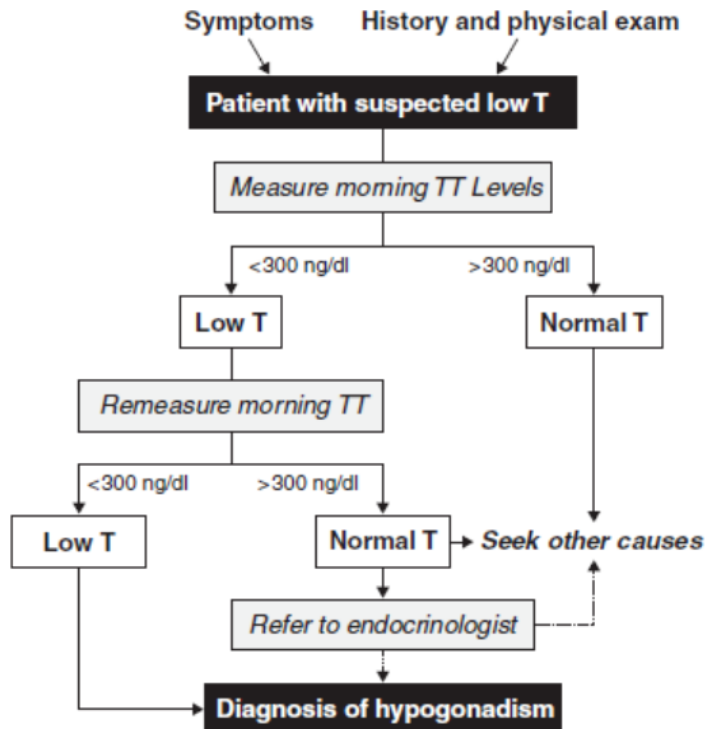
Design Features	Finkle, 2014	Vigen, 2013	Shores, 2012	Muraleedharan, 2013	Baillargeon, 2014
Design Type	(a) Retrospective self-control cohort (b) Retrospective cohort with parallel group (TRT & PDE5-I)	Retrospective cohort	Retrospective cohort	Retrospective cohort (TIMES2 trial follow-up)	Retrospective cohort
Study outcome	Non-fatal MI TRT/PDE5-I (first event)	Composite: All-cause mortality, MI and stroke (first event)	All-cause mortality	All-cause mortality. Excluded deaths within 6 months of start to follow up	Hospitalization for MI (first event)
Exposures¹ cohorts/Sample Size	⊕TRT: n=55,598 ⊕PDE5-I: n=167,279 (weighted 141,031)	⊕TRT: n=1,223 ⊖TRT: n=7,486	⊕TRT: n=398 ⊖TRT: n=633	⊕TRT: n=64 ⊖TRT: n=174	⊕TRT: n=6,455 ⊖TRT: n=19,065
Statistical Methods	Pre-TRT: 1 year; Post-TRT: 90 days (a) Self-control cohort: Post/pre RR (b) Parallel cohort: Propensity score weighting ATT ⁽⁵⁾ to estimate RR and weighted poisson regression to estimate ratio of rate ratios (RRR)	Cox regression with stabilized inverse probability of treatment weights HR (95%CI); Weighted Kaplan Meier survival curves	Cox regression analysis with Time-varying TRT HR (95%CI); Unadjusted Kaplan Meier Curves; (Propensity score analysis [exploratory analysis])	Cox regression analysis HR (95%CI); Kaplan Meier Curves	Cohort selection: matching on author's developed MI prognostic score at baseline Analysis of outcome: Cox regression analysis HR (95% CI)

Design Features	Finkle, 2014	Vigen, 2013	Shores, 2012	Muraleedharan, 2013	Baillargeon, 2014
Variables and Adjustments	Used for Propensity Score Weights and in Poisson Model: Prior Diagnoses (e.g. Heart Failure, Hyperlipidemia, Hypertension, Heart Disease, Osteoarthritis, Cardiac Symptoms, Cardiovascular disease, COPD), Prior Rx (e.g. anti-coags, anti-hypertensives, statins, NSAIDs, SSRIs, corticosteroids, diabetic meds)	Used to create weights: Age, Race, comorbidities (e.g. HTN, dyslipidemia, CHD, osteoporosis, asthma, COPD), and prior cardiovascular procedures (e.g. revascularization, catheterization, coronary bypass graft surgery) Used in weighted Cox Model: time varying TRT, CAD, interaction of CAD and TRT)	Used in Cox Model: Time varying TRT, Age, clinical site, baseline testosterone level, BMI, overall medical morbidity, hospitalization in the past year, diabetes mellitus, and coronary heart disease.	Used in Cox Model: TRT, Age, weight, height, BMI, HbA1c, pre-existing cardiovascular disease, smoking status, statin, ACE inhibitors and ARB treatment.	Used for matching: MI prognostic index score derived from 85 clinical classification codes, age, race, Medicaid eligibility and interactions term with age Used in Cox Model: TRT, Education, elixhauser comorbidity index score, indications for testosterone therapy (fatigue, hypogonadism, osteoporosis, and sexual dysfunction) and quartile of MI prognostic index score
Follow up and Treatment Duration	Follow up time: up to 90 days after 1 st Rx	Average follow up: 27.5 months Average TRT duration: Approx. 10-months	Average follow up: 40 months Average TRT duration: 20-months	Average follow up: 6 years (entire cohort) Average TRT duration: 42-months (85% of cohort >24 months)	Average duration of follow-up: about 3.5 years Median number of injections in study period: 2.5
Primary results^{2,3}	Post/Pre TRT, RR (95% CI) Overall: 1.36 (1.03, 1.81) <65 years: 1.17 (0.84, 1.63) ≥65 years: 2.19 (1.27, 3.77)	Intent to Treat HR (95% CI) 1.29 (1.04, 1.58)	Intent to Treat HR (95% CI) 0.61 (0.42, 0.88)	Intent to Treat HR (95% CI) 0.43 (0.26, 0.77)	Intent to Treat HR (95% CI): 0.84 (0.69 – 1.02)

Design Features	Finkle, 2014	Vigen, 2013	Shores, 2012	Muraleedharan, 2013	Baillargeon, 2014
Select Secondary results/sensitivity analyses	<p>Post/Pre TRT, RR (95% CI)</p> <p>⊕Heart disease <65 years 2.90 (1.49, 5.62) ≥65 years 2.16 (0.92, 5.10)</p> <p>∅Heart disease <65 years 0.90 (0.61, 1.34) ≥65 years 2.21 (1.09, 4.45)</p> <p>[Post/Pre-TRT] / [Post/Pre-PDE5-I], RRR (95% CI)</p> <p>Overall 1.27 (0.94, 1.71) <65 years 1.10 (0.78, 1.56) ≥65 years 1.90 (1.04, 3.49)</p>	Point estimate stable after additional adjustment for CAD	<p>As treated: HR 0.65 (0.39, 1.08)</p> <p>Exclusive of deaths in 1st year of follow-up (sensitivity) n=69: HR 0.47 (0.29, 0.76)</p>	Survival in ⊕TRT similar to cohort of men with normal testosterone levels with no TRT	<p>Intent to Treat HR (95% CI) by MI prognostic index score quartile</p> <p>1st quartile: HR=1.20 (0.88-1.67) 2nd quartile: HR= 0.94 (0.69-1.30) 3rd quartile: HR=0.78 (0.59-1.01) 4th quartile: HR= 0.69 (0.53-0.92)</p>
<p>¹ ⊕ indicates a drug exposed group, ∅ indicates the non-exposed group (controls)</p> <p>²These results use non exposed group as a reference. Thus, an estimate higher than 1 shows harm of TRT compared to no TRT whereas an estimate lower than 1 shows benefit of TRT compared to no TRT. Note that Muraleedharan et al used TRT as a reference and reported a HR 2.3 (1.3, 3.9).</p> <p>³ Intent to treat or ITT in this table is as described in the document, that is subjects in the cohort were included in the analysis until the event or end of follow up, not until end of treatment.</p> <p>ACE; Angiotensin converting enzyme; ATT Average treatment effect for the treated; ARB Angiotensin receptor blockers; BMI Body mass index; CAD Coronary artery disease; CI Confidence interval; CHD Coronary heart disease; COPD Chronic obstructive pulmonary disease; HbA1c Glycosylated hemoglobin; MI Myocardial infarction; ng/dL Nanograms per deciliter; NSAIDS Nonsteroidal anti-inflammatory drugs; PDE5-I Phosphodiesterase-5 inhibitor; RR Relative risk; RRR Ratio of rate ratios; SSA Social Security Administration; SSRI Selective serotonin receptor inhibitor; TRT Testosterone replacement therapy</p>					

8 APPENDIX B FIGURES

Figure 1: Algorithm for the diagnosis of hypogonadism



V. Clinical Evaluation of the Cardiovascular Events –

**Office of Drug Evaluation I,
Division of Cardiovascular and
Renal Products**

Advisory Committee

Background Package

Clinical Evaluation of the Cardiovascular Risk of Testosterone

Fred Signore MD, PhD, FACC

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Food and Drug Administration

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1 Executive Summary

The Division of Cardiovascular and Renal Products (DCRP) was asked by the Division of Bone, Reproductive and Urologic Products to provide a summary assessment of the risk of cardiovascular events associated with testosterone therapy. This review focused on the following four published studies: one randomized double-blind placebo-controlled trial (Basaria et al.), two retrospective cohort studies (Finkle et al., Vigen et al.), and one meta-analysis of 27 randomized controlled trials (Xu et al.)-refer to the joint review by the Office of Surveillance and Epidemiology, Division of Epidemiology II, and the Office of Biostatistics, Division of Biometrics VII for a more in-depth and detailed critique. A literature search was also conducted and additional studies were reviewed to further assess for a potential signal of cardiovascular harm associated with testosterone use.

Review of the studies suggest a possible safety signal of cardiovascular harm associated with testosterone use; however, a variety of caveats limit the interpretability of the evidence, including small sample sizes, low event rates, event ascertainment issues, and conflicting results that suggest that testosterone is both harmful and beneficial with respect to cardiovascular risk.

These studies do not provide conclusive evidence of increased cardiovascular risk associated with testosterone therapy.

2 Introduction

2.1 Background

FDA recently received a Citizen's Petition that put forth data from four clinical studies to support the argument that testosterone therapy is associated with increased cardiovascular risk. These studies are: a randomized clinical trial (Basaria et al.), two observational studies (Vigen et al., and Finkle et al.), and one meta-analysis (Xu et al.), all of which report an increase in cardiovascular events associated with testosterone use.

2.2 Data Sources Reviewed

DCRP received and reviewed the following materials:

- Consult from DBRUP dated 02 APRIL 2014
- Citizen Petition dated 25 FEBRUARY 2014
- Publication by Basaria et al. ([Section 3.1 Basaria et al. \(2010\)](#))

- Publication by Finkle et al. ([Section 3.2 Finkle et al. \(2014\)](#))
- Publication by Vigen et al. ([Section 3.3 Vigen et al. \(2013\)](#))
- Publication by Xu et al. ([Section 3.4 Xu et al. \(2013\)](#))
- Additional data provided by Xu et al. ([Section 3.4 Xu et al. \(2013\)](#))

3 Assessment of Evidence Regarding Potential Cardiovascular Risk with Testosterone Therapy

In addition to the four studies provided in the Citizen's Petition, independently retrieved additional studies suggested a mortality benefit for patients prescribed testosterone (i.e., Shores et al. (2012), Muraleedharan et al. (2013)).

3.1 Basaria et al. (2010)

Basaria et al. described the Testosterone in Older Men with Mobility Limitations (TOM) study, which was a randomized, double-blind, placebo-controlled, parallel group trial enrolling men ≥ 65 years old with low serum testosterone (i.e., total serum testosterone 100-350 ng/dL or free serum testosterone <50 pg/mL) who had limitations in mobility. Subjects received testosterone gel for 6 months. The efficacy endpoint was the change from baseline in maximum voluntary muscle strength in a leg press exercise. The data and safety monitoring board recommended that the trial be discontinued early, after enrollment of 209 out of the planned 252 subjects, because there was a significantly higher rate of adverse cardiovascular-related events in the testosterone group than in the placebo group. There were 106 subjects in the testosterone arm, of whom 23 had one or more cardiovascular-related adverse events. There were 103 subjects in the placebo arm, of whom 5 had one or more cardiovascular related adverse events. Examples of cardiovascular related events included chest pain, myocardial infarction, left ventricular strain, ECG-ectopy, peripheral edema, and carotid bruit. The authors stated that a structured evaluation of cardiovascular events was not performed. Using strict Major Adverse Cardiac Events (MACE), which included death, myocardial infarction, and stroke as a post-hoc exploratory endpoint, the counts were 4 MACE in the testosterone arm and 0 MACE in the placebo arm. There appeared to be a dose-response relationship between testosterone and cardiovascular risk, but it was non-conclusive because of the small number of events. The authors of this publication have explicitly indicated that the differences between the groups in cardiovascular adverse events in this small study might have been due to chance alone.

In summary, this study suggested a potential but inconclusive safety signal.

3.2 Finkle et al. (2014)

Finkle et al. conducted a retrospective cohort study to assess possible associations between testosterone therapy (TT) or PDE5 Inhibitors (PDE5I) and non-fatal myocardial infarction (MI) 90 days following an initial prescription of either drug. The database comprised 55,592 patients prescribed TT and 167,279 patients prescribed PDE5I. The baseline characteristics in each cohort appeared similar to each other. In a self-controlled cohort analysis, the rate of MI 90 days after TT was compared to the rate of MI 1 year prior to the testosterone prescription. A similar comparison was made for those patients prescribed PDE5I. The diagnostic indications for testosterone were not specified. Compliance data were not provided indicating whether or not either drug was actually consumed. There was no source verification for MI events. It is possible that the history of heart disease pre-disposed the younger patient population to testosterone mediated cardiovascular events. However, one would expect a similar finding in the subgroup of patients who were ≥ 65 years of age with a history of heart disease, but the event rates among testosterone-treated patients who were ≥ 65 years of age with a history of heart disease and without a history of heart disease were similar.

Table 1 shows the rates of myocardial infarction per 1,000 persons per year (PY) for men of all ages as well as for men < 65 years of age and ≥ 65 years of age. For patients prescribed TT, the data showed a pre-prescription MI event rate of 3.48 (95%CI 3.02-4.01) and a post-prescription rate of 4.75 (95%CI 3.72-6.05). The post/pre prescription rate ratio (RR) was 1.36 (95%CI 1.03-1.81). For patients ≥ 65 years, the pre-prescription MI event rate was 5.27 (95%CI 3.81-7.27) and the post-prescription MI event rate was 11.52 (95%CI 3.72-6.05). These event rates were respectively higher compared to patients < 65 years (i.e. pre-prescription MI event rate of 3.22 (95%CI 2.75-3.77); post-prescription MI event rate of 3.76 (95%CI 2.81-5.04)). Compared to patients prescribed testosterone, patients prescribed a PDE5I had a lower RR value for all ages and for both age categories (i.e. < 65 years and ≥ 65 years). Consequently, the ratio of the RR for testosterone over the RR for PDE5I (the relative risk ratio or RRR) was numerically but not statistically significantly greater than one. When categorizing the testosterone-prescribed patient population by age in 5 year increments (see **Table 2**), the RR results for each age group was not significant except for the population ≥ 75 years. However, from ages < 55 years to ≥ 75 years, there was a trend of increasing RR with increasing age. The sample size in each age group was unspecified and there was no adjustment for multiplicity. Similar data for the PDE5I-prescribed patient population were not presented in the manuscript.

Table 3 shows the number of MI events for TT vs. PDE5I, as a function of history of heart disease vs. no history of heart disease and as a function of age < 65 years vs. age ≥ 65 years. The data suggested a significant risk of MI in patients who were prescribed testosterone in two cohorts: those < 65 years with a history of heart disease and those ≥ 65 years with no history of heart disease. For those patients ≥ 65 years with a history of

heart disease taking testosterone, there was no significant risk for MI. It is possible that the history of heart disease pre-disposed the younger patient population to testosterone mediated cardiovascular events. However, one would expect a similar finding in the subgroup of patients who were ≥ 65 years of age with a history of heart disease, but the event rates among testosterone-treated patients who were ≥ 65 years of age with a history of heart disease and without a history of heart disease were similar.

Table 1: Rates of Myocardial Infarction per 1000 person-years (PY)

	All Ages		Age <65 years		Age ≥ 65 years	
	TT	PDE5I	TT	PDE5I	TT	PDE5I
Sample Size	55,593	141,671	48,539	121,696	7,054	19,505
<u>Pre-Rx</u>						
# cases	193	695	156	556	37	139
Rate/1000 PY (95%CI)	3.48 (3.02-4.01)	3.48 (3.02-4.01)	3.22 (2.75-3.77)	3.22 (2.75-3.77)	5.27 (3.81-7.27)	5.27 (3.81-7.27)
<u>Post-Rx</u>						
# cases	65	152	45	119	20	33
Rate/1000 PY (95%CI)	4.75 (3.72-6.05)	3.75 (3.19-4.40)	3.76 (2.81-5.04)	3.42 (2.76-4.24)	11.52 (7.43-17.86)	6.06 (4.26-8.63)
RR (95%CI)	1.36 (1.03-1.81)	1.08 (0.93-1.24)	1.17 (0.84-1.63)	1.06 (0.91-1.24)	2.19 (1.27, 3.77)	1.15 (0.83-1.59)
RRR	1.27 (0.94-1.71)		1.90 (1.04-3.49)		1.10 (0.78-1.56)	

Source: Finkle et al. (2014)-combined Tables 1, 3; RR= post/pre prescription rate ratio; RRR= ratio of the RR (RR for testosterone/RR_{for} PDE5I)

Table 2: RR_{TT} of Myocardial Infarction by age category from the Finkle Cohort Study

Age (years)	Post/Pre TT
<55	0.95 (0.54, 1.67)
55-59	1.35 (0.77, 2.38)
60-64	1.29 (0.71, 2.35)
65-69	1.35 (0.44, 4.18)
70-74	1.62 (0.51, 5.16)
≥ 75	3.43 (1.54, 7.56)

Source: Finkle et al. (2014)-Results section

Table 3: Risk of MI in patients <65 years and ≥65 years with and without a previous history of heart disease from Finkle Cohort Study

	Heart Disease History		No Heart Disease History	
	TT	PDE5I	TT	PDE5I
	Age < 65 years			
Patients (N)	4,006	10,681	44,533	130,831
Events (n)-pre TT	21	65	135	491
Events (n)-post TT	15	20	30	99
RR (95%CI)	2.90 (1.49, 5.62)	1.40 (0.91, 2.14)	0.90 (0.61, 1.34)	0.99 (0.84, 1.17)
RRR (95%CI)	2.07 (1.05, 4.11)		0.91 (0.60, 1.47)	
	Age ≥ 65 years			
Patients (N)	2,047	5,492	5,057	20,275
Events (n)-pre TT	15	35	22	104
Events (n)-post TT	8	13	12	20
RR (95%CI)	2.16 (0.92, 5.10)	1.13 (0.68, 1.88)	2.21 (1.09, 4.46)	0.92 (0.60, 1.39)
RRR (95%CI)	1.90 (0.66, 5.50)		2.41 (1.12, 5.17)	

Source: Finkle et al. (2014)-Table 4 of manuscript. Events = MI. RR = post/pre prescription MI rate; RRR = RR for testosterone divided by RR for PDE5I

In summary, this study suggested that for patients prescribed either TT or PDE5I, the rate of MI events post-prescription was higher than the rate of MI events pre-prescription, but this difference was more pronounced in the cohort prescribed TT. The data suggested an increased risk of TT-related MI events for patients <65 years with a history of heart disease compared to patients <65 years without a history of heart disease. Contrary to what was expected, the MI event rate for patients >65 years was similar for those with and without a history of heart disease. The diagnostic indications for testosterone were not specified. Compliance data were not provided and there was no source verification for MI events. Given the consequent uncertainties, the potential safety signal suggested by this study was inconclusive.

3.3 Vigen et al. (2013)

Vigen et al. conducted a retrospective cohort study to assess the association between testosterone therapy and the composite outcome comprised of overall mortality, MI, and stroke in men with low testosterone (i.e., <300 ng/dL) who also underwent coronary angiography between the years 2005-2011. The criterion for coronary artery disease as described in this publication was ≥20% lesion in any epicardial artery. The “primary cohort” (i.e. as specified in the publication but presumed individuals who were screened) consisted of 23,173 men who underwent coronary angiography between 2005 and 2011 and who had a total testosterone level checked. Of these, a total of 14,464 men were reported to have been excluded (9996 with testosterone ≥300ng/dL; 2798 receiving testosterone therapy before angiography; 1132 receiving testosterone

after MI or stroke; 397 missing coronary anatomy data; 112 receiving testosterone before testosterone was measured; 17 with hematocrit > 50%; and 12 with PSA >4ng/mL). Therefore, a total of 8,709 men were included in the study (1223 receiving testosterone and 7486 not receiving testosterone). There were 1710 events (testosterone group: 67 deaths, 23 MIs, 33 strokes; no-testosterone group: 681 deaths, 420 MIs, 486 strokes). For each type of event, the incidence was consistently lower in the testosterone group vs. the no-testosterone group, respectively (death: 5.5% vs. 9.1%; MI: 1.9% vs. 5.6%; stroke: 2.7% vs. 6.5%)—see [Table 4](#). Following adjustment of imbalances in baseline covariates, there was a statistically significant increase in the composite endpoint not favoring testosterone therapy (HR 1.29, 95%CI 1.05-1.58). The authors have identified key limitations of the study, such as “unmeasured confounding or hidden bias, unknown time of day in which blood levels were drawn for testosterone measurement, and lack of chart review validation”.

In addition to the key limitations identified by the authors, one important issue that was not accounted for was baseline testosterone level. There was a significantly lower baseline testosterone level in the testosterone group compared to the no-testosterone group. This was viewed as a significant oversight (Traish et al., 2013).

Table 4: Number of events in each cohort in Vigen retrospective study

Endpoint-number of events	Testosterone Treatment (N=1223)	No Testosterone Treatment (N=7486)
Death	67 (5.5%)	681 (9.1%)
MI	23 (1.9%)	420 (5.6%)
Stroke	33 (2.7%)	486 (6.5%)

Average follow-up time 27.5 months

In summary, due to the limitations in the study design, conclusions regarding an association between testosterone and increased cardiovascular risk could not be drawn.

3.4 Xu et al. (2013)

Xu et al. conducted a meta-analysis of 27 randomized placebo-controlled trials, spanning a 25 year period (1980-2005), involving 2994 subjects (1733 receiving testosterone and 1261 receiving placebo). The objective was to examine the overall risk of cardiovascular-related events associated with testosterone therapy. There were reportedly 180 cardiovascular-related events (an additional file specifies 181 events): 116 in the testosterone arms (6.7%) and 65 in the placebo arms (5.2%). Cardiovascular-related events “were defined as anything reported as such by the authors”. Using a fixed-effect model, the overall analysis suggested a greater risk of cardiovascular events with testosterone therapy relative to placebo: Odds Ratio of 1.54 (95% CI 1.09, 2.18). [Figure 1](#) shows the Forest Plot for the trials. The confidence

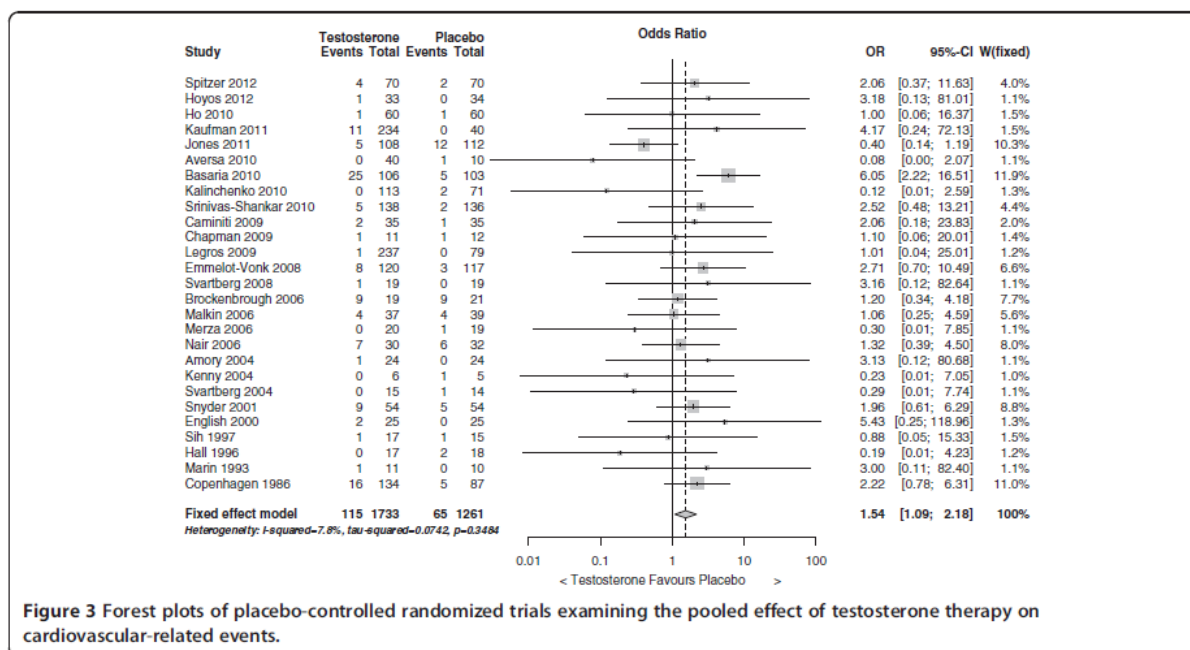
interval of the odds ratio in most of the studies crossed one, which indicates that the two arms were not statistically different regarding cardiovascular risk. The authors performed a post-hoc subgroup analysis of the trials comparing those trials funded and those trials not funded by the pharmaceutical industry. Based on the authors' stated objective, no rationale was presented to perform this subgroup analysis. This analysis was not pre-specified in the description of their analysis plan. The pharmaceutical industry reportedly funded 13 of the 27 studies. In this subgroup, there were 36 events in a total of 1020 subjects in the testosterone arms and 30 events in a total of 631 subjects in the placebo arms. A total of 14 of 27 studies were not funded by the pharmaceutical industry. In this subgroup, there were 79 events in a total of 713 subjects in the testosterone arms and 35 events in a total of 630 subjects in the placebo arms. The fixed-effect model for those trials that were **not** funded by the pharmaceutical industry suggested a greater risk of cardiovascular events with testosterone therapy relative to placebo: Odds Ratio of 2.06 (95% CI 1.34, 3.17). Similarly, using the fixed-effect model for those trials that were funded by the pharmaceutical industry, the Odds Ratio was 0.89 (95% CI 0.11, 82.40) suggesting no difference in cardiovascular risk between testosterone therapy and placebo. The confidence interval in the latter cohort is unusually large and portends significant variability. The reason for these results suggesting a funding source dependency on outcome is not clear. A non-verifiable speculative cause for these results may be the structure of adverse event reporting in the pharmaceutical industry-funded studies versus non-pharmaceutical industry-funded studies. In the former, pre-specified safety plans and data queries might have attenuated the tendency to classify cardiovascular-related events as "anything reported as such by the authors". Given the uncertainties of safety data reporting, the results of this subgroup analysis were inconclusive.

An additional file listing cardiovascular related adverse events in the 27 placebo controlled randomized clinical trials used in the meta-analysis was provided under a separate submission (see above [3.4 Xu et al. \(2013\)](#)). The cardiovascular-related adverse events included esophageal varices, splanchnic venous thrombosis, hypertension, elevated blood pressure, myocardial infarction, stroke, "other vascular events", syncope, unstable angina pectoris, frequent ventricular ectopics, phlebitis, cardiovascular complaints, hypotension, triple bypass surgery, worsening heart failure, carotid bruit, pulmonary embolism, cardiovascular involving or not involving hospitalization, death, and "no details given". Many of these events did not appear to be cardiovascular related. In order to evaluate the potential effect of testosterone on cardiovascular adverse events, FDA focused on a MACE analysis defined as the composite of all-cause mortality, myocardial infarction, and stroke. An additional MACE analysis used cardiovascular mortality instead of all-cause mortality. There was no evidence that MACE (or any of the cardiovascular-related events) were adjudicated. [Table 5](#) shows the results of the MACE analyses. There were a total of 116 CV-related events in the testosterone arms and 65 such events in the placebo arms of the trials in

the meta-analysis. There were 32 MACE (1.8%) in the testosterone arms and 18 MACE (1.4%) in the placebo arms, which included 22 vs.11 all-cause deaths, 7 vs. 4 myocardial infarctions, and 3 vs. 3 strokes in the testosterone arms and the placebo arms, respectively. When FDA analyzed MACE as the composite of cardiovascular mortality, myocardial infarction, and ischemic stroke, there were 18 MACE (1.0%) in the testosterone arms and 12 MACE (1.0%) in the placebo arms, which included 9 vs.5 deaths, 7 vs. 4 myocardial infarctions, and 2 vs. 3 strokes in the testosterone arms and the placebo arms, respectively. In comparing the number of deaths characterized as all-cause mortality vs. cardiovascular mortality, the 13 extra deaths in the testosterone arms came from bleeding esophageal varices (12) and constrictive pericarditis (1). The 6 extra deaths in the placebo arms came from esophageal varices (5) and ruptured aneurysm (1).

Although the number of all-reported CV-related adverse events was higher in the testosterone arms vs. the placebo arms, the incidence of MACE (i.e., all-cause mortality, myocardial infarction, and ischemic stroke) between the study arms was similar. When MACE was defined as cardiovascular death, myocardial infarction, and ischemic stroke, the incidence of MACE between the study arms was identical.

Figure 1: Forest plot of placebo-controlled randomized trials examining effect of testosterone on cardiovascular-related events (Xu et al.)



Source: Xu et al, Figure 3

Table 5: Adverse Event Analysis from listing associated with Xu meta-analysis

Number of reported adverse events N (%)	Testosterone (Total N=1733)	Placebo (Total N= 1261)
All events*	116 (6.7%)	65 (5.2%)
All events designated as serious	57 (3.3%)	28 (2.2%)
MACE (includes all-cause mortality, myocardial infarction, stroke)	32 (1.8%)	18 (1.4%)
MACE (includes cardiovascular death, myocardial infarction, ischemic stroke)	18 (1.0%)	12 (1.0%)
-all cause death	22 (1.3%)	11(0.9%)
-cardiovascular death	9 (0.5%)	5 (0.4%)
-myocardial infarction	7 (0.4%)	4 (0.3%)
-stroke (ischemic stroke + cerebral hemorrhage)	3 (0.2%)	3 (0.2%)
-ischemic stroke	2 (0.1%)	3 (0.2%)

**Note: Source of all events is the Additional File 4 from the meta-analysis. Source of analysis: DCRP review of each data item and extraction of MACE from list of pooled adverse events. Cerebral hemorrhage was not counted as an ischemic stroke. When using “all-cause mortality”, the 13 extra deaths in the testosterone arms came from bleeding esophageal varices (12) and constrictive pericarditis (1). The 6 extra deaths in the placebo arms came from esophageal varices (5) and ruptured aneurysm (1).*

In summary, this meta-analysis did not definitively demonstrate an increased cardiovascular risk associated with testosterone therapy.

3.5 Other Studies Supporting Testosterone Benefit or Lack of Risk

There are other studies that have suggested either an apparent cardiovascular benefit of testosterone therapy or an absence of a cardiovascular risk with testosterone therapy.

Shores et al. (2012) designed an observational study to examine the association between testosterone treatment and mortality in men with low testosterone. The database was retrieved from seven Northwest Veterans Affairs medical centers and included a cohort of 1031 male veterans older than 40 years with low testosterone (<250 ng/dL). In this study, testosterone treatment was associated with a decreased mortality compared with no testosterone treatment (Hazard Ratio 0.61, 95%CI 0.42-0.88). Similarly, in a prospective follow-up from a previously reported cohort, Muraleedharan et al. (2013) concluded that low untreated testosterone levels predicted an increase in all-cause mortality during long-term follow-up, and that testosterone replacement may improve survival in hypogonadal men with type 2 diabetes mellitus. In

a systematic review and meta-analysis of 30 randomized placebo-controlled trials examining the effect of testosterone use on cardiovascular events and risk factors in men with different degrees of androgen deficiency, Haddad et al. (2007) concluded that the currently available evidence weakly supported the conclusion that testosterone use in men was not associated with important cardiovascular effects.

4 Summary and Conclusion

The publications presented for review suggested a possible cardiovascular safety signal associated with testosterone therapy. However, each of the studies had major limitations, precluding the ability to draw definitive conclusions.

The authors of the TOM study (Basaria et al.) have explicitly indicated that the differences between the groups in cardiovascular adverse events based on low event rates might have been due to chance alone.

In the retrospective study (Finkle et al.), the results suggested a risk in patients ≥ 65 years of age and in patients < 65 years of age with pre-existing cardiovascular disease. Contrary to what one might have expected, there was no demonstrable risk for patients ≥ 65 years old who had a history of cardiovascular disease. The diagnostic indications for testosterone were not specified. Compliance data were not provided indicating whether or not either drug was actually consumed. There was no source verification for MI events.

In the retrospective study (Vigen et al.), the data themselves did not support a testosterone mediated cardiovascular risk. Prior to statistical adjustments, testosterone treatment appeared favorable compared to placebo with regard to CV outcomes. Following adjustment for imbalances, the results were nominally significant not favoring testosterone. The authors explicitly identified key limitations such as “unmeasured confounding or hidden bias, unknown time of day in which blood levels were drawn for testosterone measurement, and lack of chart review validation”. An additional limitation was not accounting for baseline testosterone.

In the meta-analysis (Xu et al.), based on data that included any adverse event related to the cardiovascular system, there was a nominal difference between testosterone and placebo when using a fixed effect model. There was no evidence that any of the data were adjudicated. When FDA counted MACE from the pooled events from the data provided, there was essentially no difference between testosterone and placebo groups.

Other publications suggested a benefit for testosterone in reducing mortality in patients with low testosterone.

In conclusion, these studies do not provide conclusive evidence of increased cardiovascular risk associated with the use of testosterone therapy.

5 References

Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy: Testosterone and Aging Clinical Research Direction, 2004, Washington: The National Academies Press

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VI. Memorandum -

**Office of Prescription Drug
Promotion, Division of Consumer
Drug Promotion**

Memorandum

Date: August 14, 2014

To: Chair, Members, and Invited Guests
Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

From: Trung-Hieu Brian Tran, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Robert Dean, MBA
Director, Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: Office of Prescription Drug Promotion: Testosterone Replacement Therapy

I. Background

Regulatory Authority

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives the FDA regulatory authority over the labeling and advertising of prescription drugs. Under the FD&C Act, a prescription drug is misbranded if, among other things, its labeling or advertising is false or misleading. In addition, a drug may be misbranded if the labeling or advertising fails to reveal material facts, including material facts about the consequences which may result from the use of the drug as suggested in the labeling or advertising. The Office of Prescription Drug Promotion (OPDP) has a Regulatory Information website that includes information on pertinent laws, regulations, and guidances.¹

The mission of OPDP is to protect the public health by ensuring that prescription drug information is truthful, balanced and accurately

¹ Available at:
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm>

communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers.

Disease Awareness Communications

Disease awareness communications are communications disseminated to consumers or healthcare practitioners that discuss a particular disease or health condition, but do not mention any specific drug or make any representation or suggestion concerning a particular drug. Disease awareness communications can provide important health information to consumers and healthcare practitioners, and can encourage consumers to seek, and healthcare practitioners to provide, appropriate treatment. Unlike drug promotional materials, disease awareness communications are not subject to the requirements of the FD&C Act and FDA regulations.

Product Claim Promotional Materials

Product claim promotional materials discuss both the name of a drug and its benefits and risks, including the indication, and should comply with the FD&C Act and FDA regulations.

As discussed in the Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion,² the language used in promotional materials to communicate benefits and risks should be comprehensible to the target audience to be considered accurate and non-misleading. For example, promotional materials directed to professionals can describe benefits and risks in medical language. However, promotional materials directed to consumers should convey benefits and risks in language understandable to consumers (i.e., clear, understandable, and non-technical).

II. Testosterone Promotion

Disease Awareness Communications and Product Claim Promotional Materials

Examples of disease awareness communications and product claim promotional materials for testosterone replacement therapy will be shown during the FDA presentation at the Joint Advisory Committee meeting on September 17, 2014.

² Available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>

Enforcement Actions

The FDA does not regulate or have enforcement authority over disease awareness communications.

The FDA does regulate product claim promotional materials and has taken action in three instances where testosterone promotional materials have violated the FD&C Act and FDA regulations.

- An untitled letter was issued on April 25, 1997, regarding an Androgel news release. The news release violated the FD&C Act and FDA regulations by promoting Androgel, an investigational drug, as safe and effective for the use under investigation. The news release also listed several other “potential uses,” such as the treatment of geriatric hypogonadism in elderly men and treatment for postmenopausal women.
- An untitled letter was issued on November 25, 1998, regarding an Androderm leaflet and Dear Doctor Letter. The Dear Doctor Letter violated the FD&C Act and FDA regulations by suggesting that Androderm was safe and effective for treating patients with non-insulin dependent diabetes mellitus (NIDDM).
- A warning letter was issued on March 24, 2010, regarding a Testopel sales aid, webpages, and video. Among other violations, the warning letter cited Testopel for promoting unapproved uses, by suggesting in the webpages several new “intended uses” for Testopel that the drug is not approved to treat (e.g., symptoms of depression, erectile dysfunction, type 2 diabetes, HIV, mood disorders, and loss in sexual interest). The webpages also suggested that Testopel treatment results in an increase in muscle mass and bone strength. Additionally, the video also promoted unapproved uses of Testopel by misleadingly implying that Testopel can be used to treat sexual dysfunction and has a positive impact on the enhancement of athletic performance of professional (and non-professional) athletes. The promotional pieces were also cited for broadening the indication, by failing to disclose the full indication for Testopel, including the important limitations to the indication.

III. Conclusion

- Disease awareness communications can educate and encourage consumers to seek appropriate medical treatment. OPDP has received complaints regarding disease awareness communications for hypogonadism. However, these communications are not subject to the requirements of the FD&C Act and FDA regulations.
- Promotional materials for all prescription products, including testosterone replacement therapies, should comply with the FD&C Act and FDA

regulations. Over the past several years, there has been an increase in the submission of promotional materials to OPDP for testosterone replacement therapy.

VII. References

References:

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VIII. Physician Labeling and Medication Guides

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDROGEL 1.62% safely and effectively. See full prescribing information for ANDROGEL 1.62%.

AndroGel® (testosterone gel) 1.62% for topical use CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning.

- Virilization has been reported in children who were secondarily exposed to testosterone gel (5.2, 6.2).
- Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel (2.2, 5.2).
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17).

RECENT MAJOR CHANGES

Warnings and Precautions (5.4) 06/2014

INDICATIONS AND USAGE

AndroGel 1.62% is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Important limitations of use:

- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established. (1, 8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

DOSAGE AND ADMINISTRATION

- Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)
- Starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet), applied topically once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of the shoulders and upper arms. Do not apply AndroGel 1.62% to any other parts of the body including the abdomen or genitals. (2.2, 12.3)
- Dose adjustment: AndroGel 1.62% can be dose adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). The dose should be titrated based on the pre-dose morning serum testosterone concentration at approximately 14 days and 28 days after starting treatment or following dose adjustment. Additionally, serum testosterone concentration should be assessed periodically thereafter. (2.1)
- Patients should wash hands immediately with soap and water after applying AndroGel 1.62% and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)

DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1.62% for topical use is available as follows:

- a metered-dose pump that delivers 20.25 mg testosterone per actuation. (3)
- packets containing 20.25 mg testosterone. (3)
- packets containing 40.5 mg testosterone. (3)

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected prostate cancer (4, 5.1)
- Pregnant or breast-feeding women. Testosterone may cause fetal harm (4, 8.1, 8.3)

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1.62%. Secondary exposure to testosterone can produce signs of virilization. AndroGel 1.62% should be discontinued until the cause of virilization is identified (5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Exogenous administration of androgens may lead to azoospermia (5.6)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.8)
- Sleep apnea may occur in those with risk factors (5.10)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.7, 5.11)
- AndroGel 1.62% is flammable until dry (5.14)

ADVERSE REACTIONS

The most common adverse reaction (incidence $\geq 5\%$) is an increase in prostate specific antigen (PSA). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended (7.2)
- Use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3)

USE IN SPECIFIC POPULATIONS

There are insufficient long-term safety data in geriatric patients using AndroGel 1.62% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2014

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel** *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel** *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use** *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.

1 INDICATIONS AND USAGE

AndroGel 1.62% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Important limitations of use:

- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure *[see Indications and Usage (1), and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet) applied topically once daily in the morning to the shoulders and upper arms.

The dose can be adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). To ensure proper dosing, the dose should be titrated based on the pre-dose morning serum testosterone concentration from a single blood draw at approximately 14 days and 28 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. [Table 1](#) describes the dose adjustments required at each titration step.

Table 1: Dose Adjustment Criteria

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)

The application site and dose of AndroGel 1.62% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AndroGel 1.62% should be applied to clean, dry, intact skin of the upper arms and shoulders. Do not apply AndroGel 1.62% to any other parts of the body, including the abdomen or genitals [*see Clinical Pharmacology (12.3)*]. Area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt. Patients should be instructed to use the palm of the hand to apply AndroGel 1.62% and spread across the maximum surface area as directed in [Table 2](#) (for pump) and [Table 3](#) (for packets) and in [Figure 1](#).

Table 2: Application Sites for AndroGel 1.62%, Pump

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0
40.5 mg	2	1	1
60.75 mg	3	2	1
81 mg	4	2	2

Table 3: Application Sites for AndroGel 1.62%, Packets

Total Dose of Testosterone	Total packets	Gel Applications Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	One 20.25 mg packet	One 20.25 mg packet	0
40.5 mg	One 40.5 mg packet	Half of contents of One 40.5 mg packet	Half of contents of One 40.5 mg packet
60.75 mg	One 20.25 mg packet AND One 40.5 mg packet	One 40.5 mg packet	One 20.25 mg packet
81 mg	Two 40.5 mg packets	One 40.5 mg packet	One 40.5 mg packet

The prescribed daily dose of AndroGel 1.62% should be applied to the right and left upper arms and shoulders as shown in the shaded areas in [Figure 1](#).

**Figure 1. Application Sites for AndroGel 1.62%**

Once the application site is dry, the site should be covered with clothing [see *Clinical Pharmacology* (12.3)]. Wash hands thoroughly with soap and water. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including AndroGel 1.62%, are flammable.

The patient should avoid swimming or showering or washing the administration site for a minimum of 2 hours after application [see *Clinical Pharmacology* (12.3)].

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for every 20.25 mg of AndroGel 1.62%. AndroGel 1.62% should be delivered directly into the palm of the hand and then applied to the application sites.

When using packets, the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. When 40.5 mg packets need to be split between the

left and right shoulder, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied. Alternatively, AndroGel 1.62% can be applied directly to the application sites from the pump or packets.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AndroGel 1.62%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1.62%.
- AndroGel 1.62% should only be applied to the upper arms and shoulders. The area of application should be limited to the area that will be covered by a short sleeve t-shirt.
- Patients should wash their hands with soap and water immediately after applying AndroGel 1.62%.
- Patients should cover the application site(s) with clothing (e.g., a t-shirt) after the gel has dried.
- Prior to situations in which direct skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AndroGel 1.62% has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

3 DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1.62% for topical use only, is available as follows:

- A metered-dose pump. Each pump actuation delivers 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 40.5 mg of testosterone in 2.5 g of gel.

4 CONTRAINDICATIONS

- AndroGel 1.62% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].
- AndroGel 1.62% is contraindicated in women who are or may become pregnant, or who are breastfeeding. AndroGel 1.62% may cause fetal harm when administered to a pregnant woman. AndroGel 1.62% may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with AndroGel 1.62%. If a pregnant woman is exposed to AndroGel 1.62%, she should be apprised of the potential hazard to the fetus [*see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluation of patients for prostate cancer prior to initiating and during treatment with androgens is appropriate [see *Contraindications* (4)].

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AndroGel 1.62% [see *Dosage and Administration* (2.2), *Use in Specific Populations* (8.1) and *Clinical Pharmacology* (12.3)].

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone gel should also be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization has been identified.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating treatment. It would also be appropriate to re-evaluate the hematocrit 3 to 6 months after starting treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products such as AndroGel 1.62%. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AndroGel 1.62% and initiate appropriate workup and management [see *Adverse Reactions* (6.2)].

5.5 Use in Women

Due to the lack of controlled evaluations in women and potential virilizing effects, AndroGel 1.62% is not indicated for use in women [*see Contraindications (4) and Use in Specific Populations (8.1, 8.3)*].

5.6 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AndroGel 1.62%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

5.7 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AndroGel 1.62% is not known to cause these adverse effects.

5.8 Edema

Androgens, including AndroGel 1.62%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease [*see Adverse Reactions (6.2)*].

5.9 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1.62%, for hypogonadism.

5.10 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

5.11 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.12 Hypercalcemia

Androgens, including AndroGel 1.62 %, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.13 Decreased Thyroxine-binding Globulin

Androgens, including AndroGel 1.62%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3

and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.14 Flammability

Alcohol based products, including AndroGel 1.62%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the AndroGel 1.62% has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AndroGel 1.62% was evaluated in a two-phase, 364-day, controlled clinical study. The first phase was a multi-center, randomized, double-blind, parallel-group, placebo-controlled period of 182 days, in which 234 hypogonadal men were treated with AndroGel 1.62% and 40 received placebo. Patients could continue in an open-label, non-comparative, maintenance period for an additional 182 days [see *Clinical Studies* (14.1)].

The most common adverse reaction reported in the double-blind period was increased prostate specific antigen (PSA) reported in 26 AndroGel 1.62%-treated patients (11.1%). In 17 patients, increased PSA was considered an adverse event by meeting one of the two pre-specified criteria for abnormal PSA values, defined as (1) average serum PSA >4 ng/mL based on two separate determinations, or (2) an average change from baseline in serum PSA of greater than 0.75 ng/mL on two determinations.

During the 182-day, double-blind period of the clinical trial, the mean change in serum PSA value was 0.14 ng/mL for patients receiving AndroGel 1.62% and -0.12 ng/mL for the patients in the placebo group. During the double-blind period, seven patients had a PSA value >4.0 ng/mL, four of these seven patients had PSA less than or equal to 4.0 ng/mL upon repeat testing. The other three patients did not undergo repeat PSA testing.

During the 182-day, open-label period of the study, the mean change in serum PSA values was 0.10 ng/mL for both patients continuing on active therapy and patients transitioning onto active from placebo. During the open-label period, three patients had a serum PSA value > 4.0 ng/mL, two of whom had a serum PSA less than or equal to 4.0 ng/mL upon repeated testing. The other patient did not undergo repeat PSA testing. Among previous placebo patients, 3 of 28 (10.7%), had increased PSA as an adverse event in the open-label period.

Table 4 shows adverse reactions reported by >2% of patients in the 182-day, double-blind period of the AndroGel 1.62% clinical trial and more frequent in the AndroGel 1.62% treated group versus placebo.

Table 4: Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of AndroGel 1.62% Clinical Trial

Adverse Reaction	Number (%) of Patients	
	AndroGel 1.62% N=234	Placebo N=40
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%
<p>*PSA increased includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.</p> <p>**Emotional lability includes: mood swings, affective disorder, impatience, anger, and aggression.</p> <p>***Contact dermatitis includes: 4 patients with dermatitis at non-application sites.</p>		

Other adverse reactions occurring in less than or equal to 2% of AndroGel 1.62%-treated patients and more frequently than placebo included: frequent urination, and hyperlipidemia.

In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis. Other adverse reactions reported by less than or equal to 2% of patients included increased hemoglobin or hematocrit, hypertension, acne, libido decreased, insomnia, and benign prostatic hypertrophy.

During the 182-day, double-blind period of the clinical trial, 25 AndroGel 1.62%-treated patients (10.7%) discontinued treatment because of adverse reactions. These adverse reactions included 17 patients with PSA increased and 1 report each of: hematocrit increased, blood pressure increased, frequent urination, diarrhea, fatigue, pituitary tumor, dizziness, skin erythema and skin nodule (same patient – neither at application site), vasovagal syncope, and diabetes mellitus. During the 182-day, open-label period, 9 patients discontinued treatment because of adverse reactions. These adverse reactions included 6 reports of PSA increased, 2 of hematocrit increased, and 1 each of triglycerides increased and prostate cancer.

Application Site Reactions

In the 182-day double-blind period of the study, application site reactions were reported in two (2/234; 0.9%) patients receiving AndroGel 1.62%, both of which resolved. Neither of these patients discontinued the study due to application site adverse reactions. In the open-label period of the study, application site reactions were reported in three (3/219; 1.4%) additional patients that were treated with AndroGel 1.62%. None of these subjects were discontinued from the study due to application site reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel 1%. Because the reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (Table 5).

Table 5: Adverse Reactions from Post Approval Experience of AndroGel 1% by System Organ Class

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders:	Elevated hemoglobin or hematocrit, polycythemia, anemia
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination*
Hepatobiliary disorders:	Abnormal liver function tests
Investigations:	Lab test abnormal**, elevated PSA, electrolyte changes (nitrogen, calcium, potassium [includes hypokalemia], phosphorus, sodium), impaired glucose tolerance, hyperlipidemia, HDL, fluctuating testosterone levels, weight increase
Neoplasms:	Prostate cancer
Nervous system disorders:	Dizziness, headache, insomnia, sleep apnea
Psychiatric disorders:	Amnesia, anxiety, depression, hostility, emotional lability, decreased libido, nervousness
Reproductive system and breast disorders:	Gynecomastia, mastodynia, oligospermia, priapism (frequent or prolonged erections), prostate enlargement, BPH, testis disorder***
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (discolored hair, dry skin, erythema, paresthesia, pruritus, rash), skin dry, pruritus, sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes), venous thromboembolism
<p>* Impaired urination includes nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream</p> <p>**Lab test abnormal includes elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, or elevated serum creatinine</p> <p>***Testis disorder includes atrophy or non-palpable testis, varicocele, testis sensitivity or tenderness</p>	

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or the penis, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. In a few cases, however, enlarged genitalia did not fully return to age appropriate normal size, and bone age remained modestly greater than chronological age. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/or other fabric, such as towels and sheets [*see Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may decrease insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Contraindications (4)*]: AndroGel 1.62% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AndroGel 1.62% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation [*see Contraindications (4)*].

8.4 Pediatric Use

The safety and effectiveness of AndroGel 1.62% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel 1.62% to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 234 patients enrolled in the clinical trial utilizing AndroGel 1.62%, 21 were over 65 years of age. Additionally, there is insufficient long-term safety data in geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

8.6 Renal Impairment

No studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AndroGel 1.62% contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drugs are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of a withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

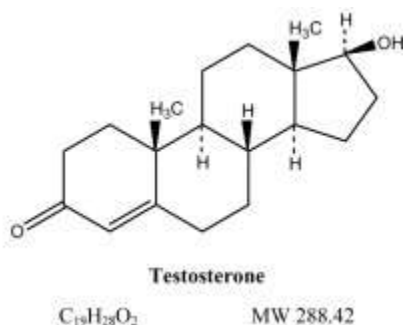
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdosage in the AndroGel 1.62% clinical trial.

Treatment of overdosage would consist of discontinuation of AndroGel 1.62%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

AndroGel 1.62% for topical use is a clear, colorless gel containing testosterone. Testosterone is an androgen. AndroGel 1.62% is available in a metered-dose pump or unit dose packets.

The active pharmacologic ingredient in AndroGel 1.62% is testosterone. Testosterone USP is a white to almost white powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



The inactive ingredients in AndroGel 1.62% are: carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal chord thickening; and alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia while secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AndroGel 1.62%.

12.3 Pharmacokinetics

Absorption

AndroGel 1.62% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300 – 1000 ng/dL) seen in healthy men. AndroGel 1.62% provides continuous transdermal delivery of testosterone for 24 hours following once daily application to clean, dry, intact skin of the shoulders and upper arms. Average serum testosterone concentrations over 24 hours (C_{avg}) observed when AndroGel 1.62% was applied to the upper arms/shoulders were comparable to average serum testosterone concentrations (C_{avg}) when AndroGel 1.62% was applied using a rotation method utilizing the abdomen and upper arms/shoulders. The rotation of abdomen and upper arms/shoulders was a method used in the pivotal clinical trial [see *Clinical Studies* (14.1)].

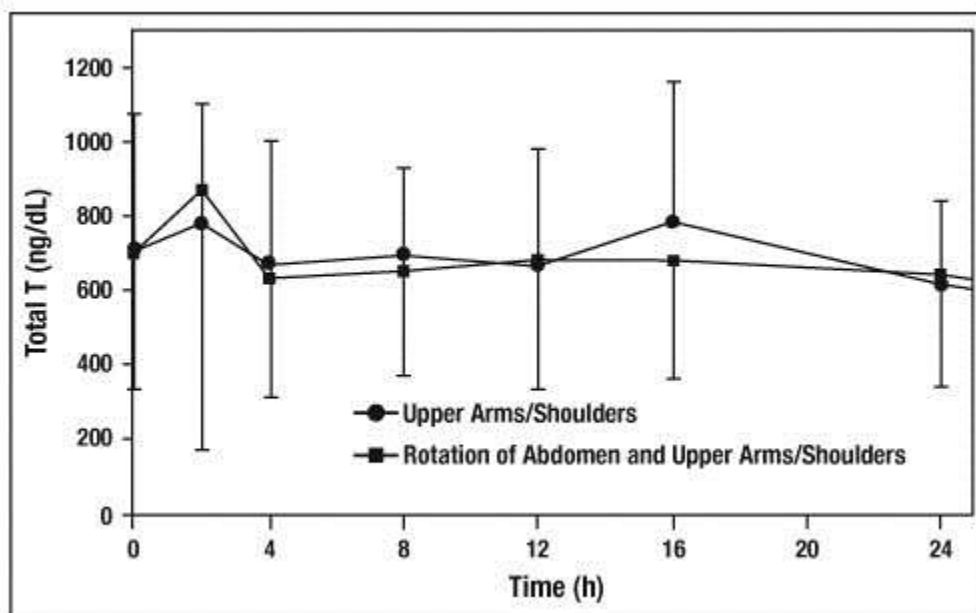


Figure 2: Mean (\pm SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following AndroGel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days

Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

Excretion

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

When AndroGel 1.62% treatment is discontinued, serum testosterone concentrations return to approximately baseline concentrations within 48-72 hours after administration of the last dose.

Potential for testosterone transfer

The potential for testosterone transfer following administration of AndroGel 1.62% when it was applied only to upper arms/shoulders was evaluated in two clinical studies of males dosed with AndroGel 1.62% and their untreated female partners. In one study, 8 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes. Serum concentrations of testosterone were monitored in female subjects for 24 hours after contact occurred. After direct skin-to-skin contact with the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 280% and 267%, respectively, compared to mean baseline testosterone concentrations. In a second study evaluating transfer of testosterone, 12 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes while the site of application was covered by a t-shirt. When a t-shirt was used to cover the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 6% and 11%, respectively, compared to mean baseline testosterone concentrations.

A separate study was conducted to evaluate the potential for testosterone transfer from 16 males dosed with AndroGel 1.62% 81 mg when it was applied to abdomen only for 7 days, a site of application not approved for AndroGel 1.62%. Two (2) hours after application to the males on each day, the female subjects rubbed their abdomens for 15 minutes to the abdomen of the males. The males had covered the application area with a T-shirt. The mean testosterone C_{avg} and C_{max} in female subjects on day 1 increased by 43% and 47%, respectively, compared to mean baseline testosterone concentrations. The mean testosterone C_{avg} and C_{max} in female subjects on day 7 increased by 60% and 58%, respectively, compared to mean baseline testosterone concentrations.

Effect of showering

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 24 hypogonadal men, the effect of showering on testosterone exposure was assessed after once daily application of AndroGel 1.62% 81 mg to upper arms/shoulders for 7 days in each treatment period. On the 7th day of each treatment period, hypogonadal men took a shower with soap and water at either 2, 6, or 10 hours after drug application. The effect of showering at 2 or 6 hours post-dose on Day 7 resulted in 13% and 12% decreases in mean C_{avg} , respectively, compared to

Day 6 when no shower was taken after drug application. Showering at 10 hours after drug application had no effect on bioavailability. The amount of testosterone remaining in the outer layers of the skin at the application site on the 7th day was assessed using a tape stripping procedure and was reduced by at least 80% after showering 2-10 hours post-dose compared to on the 6th day when no shower was taken after drug application.

Effect of sunscreen or moisturizing lotion on absorption of testosterone

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 18 hypogonadal males, the effect of applying a moisturizing lotion or a sunscreen on the absorption of testosterone was evaluated with the upper arms/shoulders as application sites. For 7 days, moisturizing lotion or sunscreen (SPF 50) was applied daily to the AndroGel 1.62% application site 1 hour after the application of AndroGel 1.62% 40.5 mg. Application of moisturizing lotion increased mean testosterone C_{avg} and C_{max} by 14% and 17%, respectively, compared to AndroGel 1.62% administered alone. Application of sunscreen increased mean testosterone C_{avg} and C_{max} by 8% and 13%, respectively, compared to AndroGel 1.62% applied alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hypogonadal Males

AndroGel 1.62% was evaluated in a multi-center, randomized, double-blind, parallel-group, placebo-controlled study (182-day double-blind period) in 274 hypogonadal men with body mass index (BMI) 18-40 kg/m² and 18-80 years of age (mean age 53.8 years). The patients had an average serum testosterone concentration of <300 ng/dL, as determined by two morning samples collected on the same visit. Patients were Caucasian 83%, Black 13%, Asian or Native American 4%. 7.5% of patients were Hispanic.

Patients were randomized to receive active treatment or placebo using a rotation method utilizing the abdomen and upper arms/shoulders for 182 days. All patients were started at a daily dose of 40.5 mg (two pump actuations) AndroGel 1.62% or matching placebo on Day 1 of the study. Patients returned to the clinic on Day 14, Day 28, and Day 42 for predose serum total testosterone assessments. The patient's daily dose was titrated up or down in 20.25 mg increments if the predose serum testosterone value was outside the range of 350-750 ng/dL. The

study included four active AndroGel 1.62% doses: 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg daily.

The primary endpoint was the percentage of patients with C_{avg} within the normal range of 300-1000 ng/dL on Day 112. In patients treated with AndroGel 1.62%, 81.6% (146/179) had C_{avg} within the normal range at Day 112. The secondary endpoint was the percentage of patients, with C_{max} above three pre-determined limits. The percentages of patients with C_{max} greater than 1500 ng/dL, and between 1800 and 2499 ng/dL on Day 112 were 11.2% and 5.5%, respectively. Two patients had a $C_{max} > 2500$ ng/dL on Day 112 (2510 ng/dL and 2550 ng/dL, respectively); neither of these 2 patients demonstrated an abnormal C_{max} on prior or subsequent assessments at the same dose.

Patients could agree to continue in an open-label, active treatment maintenance period of the study for an additional 182 days.

Dose titrations on Days 14, 28, and 42 resulted in final doses of 20.25 mg – 81 mg on Day 112 as shown in [Table 6](#).

Table 6: Mean (SD) Testosterone Concentrations (C_{avg} and C_{max}) by final dose on Days 112 and 364

Parameter	Final Dose on Day 112					All Active (n=179)
	Placebo (n=27)	20.25 mg (n=12)	40.5 mg (n=34)	60.75 mg (n=54)	81 mg (n=79)	
C_{avg} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	813 (479)	845 (480)
	Final Dose on Day 364					Continuing Active (n=136)
		20.25 mg (n=7)	40.5 mg (n=26)	60.75 mg (n=29)	81 mg (n=74)	
C_{avg} (ng/dL)		386 (130)	474 (176)	513 (222)	432 (186)	455 (192)
C_{max} (ng/dL)		562 (187)	715 (306)	839 (568)	649 (329)	697 (389)

[Figure 3](#) summarizes the pharmacokinetic profile of total testosterone in patients completing 112 days of AndroGel 1.62% treatment administered as a starting dose of 40.5 mg of testosterone (2 pump actuations) for the initial 14 days followed by possible titration according to the follow-up testosterone measurements.

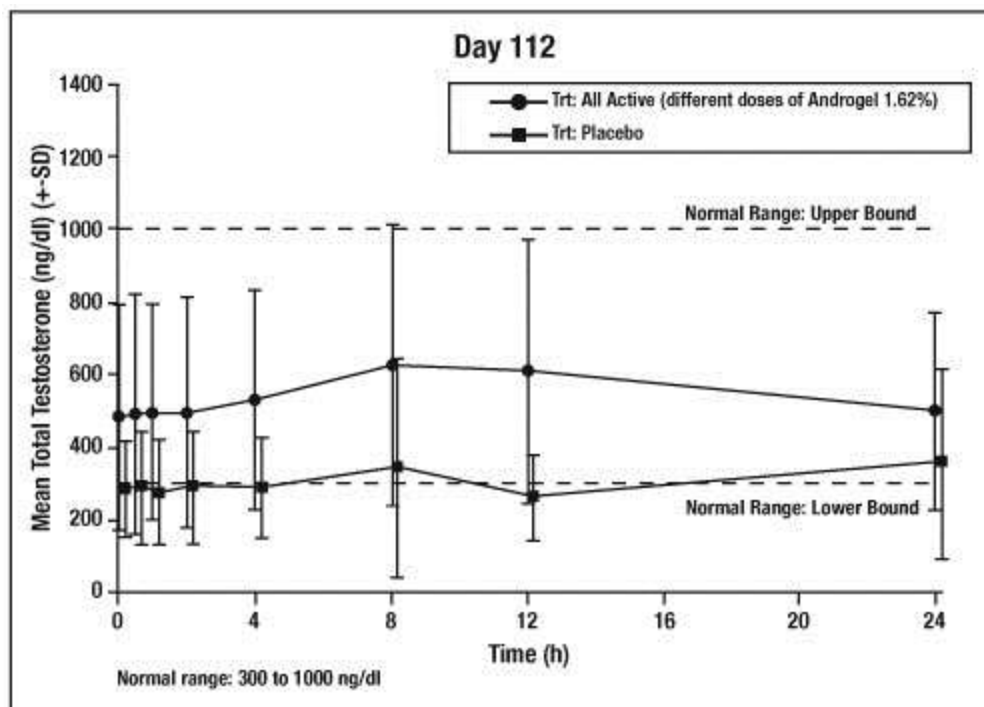


Figure 3: Mean (\pm SD) Steady-State Serum Total Testosterone Concentrations on Day 112

Efficacy was maintained in the group of men that received AndroGel 1.62% for one full year. In that group, 78% (106/136) had average serum testosterone concentrations in the normal range at Day 364. [Figure 4](#) summarizes the mean total testosterone profile for these patients on Day 364.

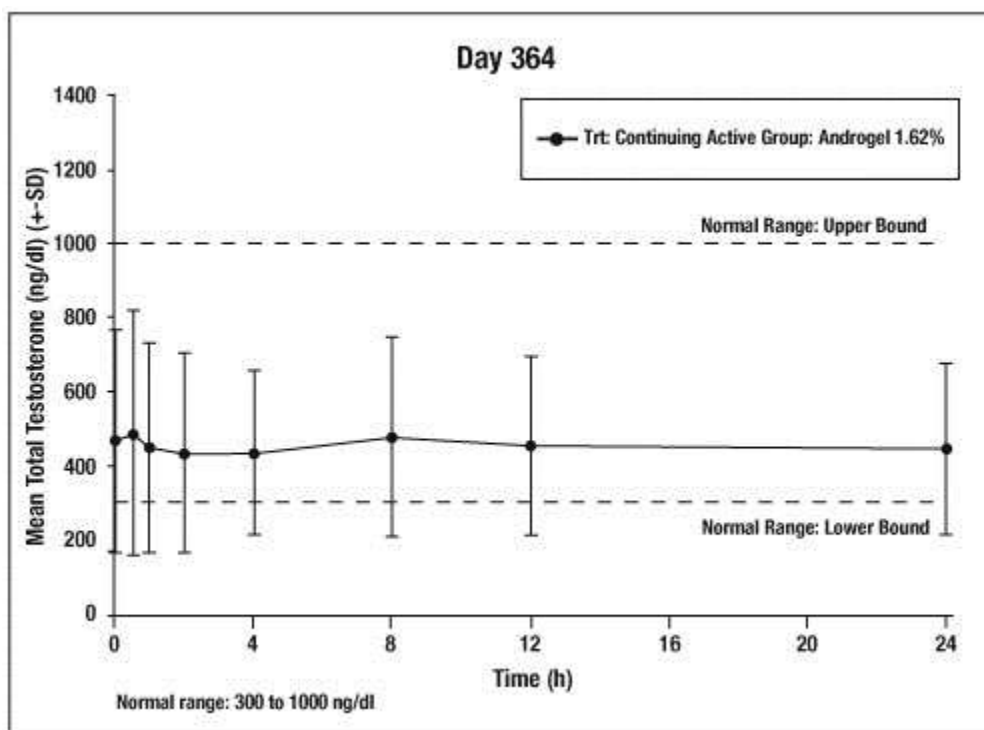


Figure 4: Mean (\pm SD) Steady-State Serum Total Testosterone Concentrations on Day 364

The mean estradiol and DHT concentration profiles paralleled the changes observed in testosterone. The levels of LH and FSH decreased with testosterone treatment. The decreases in levels of LH and FSH are consistent with reports published in the literature of long-term treatment with testosterone.

16 HOW SUPPLIED/STORAGE AND HANDLING

AndroGel 1.62% is supplied in non-aerosol, metered-dose pumps that deliver 20.25 mg of testosterone per complete pump actuation. The pumps are composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations; each pump actuation dispenses 1.25 g of gel.

AndroGel 1.62% is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 1.25 g or 2.5 g gel contains 20.25 mg or 40.5 mg testosterone, respectively.

NDC Number	Package Size
0051-8462-33	88 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 20.25 mg of testosterone in 1.25 g of gel)
0051-8462-12	Each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel
0051-8462-31	30 packets (each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel)
0051-8462-01	Each unit dose packet contains 40.5 mg of testosterone provided in 2.5 g of gel
0051-8462-30	30 packets (each unit dose packet contains 40.5 mg of testosterone provided in 2.5 g of gel)

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°- 30°C (59°- 86°F) [see USP Controlled Room Temperature].

Used AndroGel 1.62% pumps or used AndroGel 1.62% packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

Patients should be informed of the following:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use AndroGel 1.62% [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men. Cases of secondary exposure to testosterone have been reported in children.

Physicians should advise patients of the reported signs and symptoms of secondary exposure, which may include the following:

- In children: unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.
- In women: changes in hair distribution, increase in acne, or other signs of testosterone effects.
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider.
- AndroGel 1.62% should be promptly discontinued until the cause of virilization is identified.

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from AndroGel 1.62% in men [see *Medication Guide*]:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using AndroGel 1.62%.
- Patients using AndroGel 1.62% should apply the product as directed and strictly adhere to the following:
 - **Wash hands** with soap and water immediately after application.
 - **Cover the application site(s)** with clothing after the gel has dried.
 - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
- In the event that unwashed or unclothed skin to which AndroGel 1.62% has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting the urine stream, passing urine many times during the day, having an urge to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.

- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should Be Advised of the Following Instructions for Use

- Read the **Medication Guide** before starting AndroGel 1.62% therapy and to reread it each time the prescription is renewed.
- AndroGel 1.62% should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.
- Keep AndroGel 1.62% out of the reach of children.
- AndroGel 1.62% is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried.
- It is important to adhere to all recommended monitoring.
- Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.
- AndroGel 1.62% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1.62% with anyone.
- Wait 2 hours before swimming or washing following application of AndroGel 1.62%. This will ensure that the greatest amount of AndroGel 1.62% is absorbed into their system.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA

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Medication Guide

ANDROGEL[®] (AN DROW JEL) CIII (testosterone gel) 1.62%

Read this Medication Guide before you start using ANDROGEL 1.62% and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ANDROGEL 1.62%?

- 1. Early signs and symptoms of puberty have happened in young children who were accidentally exposed to testosterone through contact with men using ANDROGEL 1.62%.**

Signs and symptoms of early puberty in a child may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive

- aggressive behavior

ANDROGEL 1.62% can transfer from your body to others.

2. **Women and children should avoid contact with the unwashed or unclothed area where ANDROGEL 1.62% has been applied to your skin.**

Stop using ANDROGEL 1.62% and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to ANDROGEL 1.62%.

Signs and symptoms of exposure to ANDROGEL 1.62% in children may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive
- aggressive behavior

Signs and symptoms of exposure to ANDROGEL 1.62% in women may include:

- changes in body hair
 - a large increase in acne
- **To lower the risk of transfer of ANDROGEL 1.62% from your body to others, you should follow these important instructions:**
 - Apply ANDROGEL 1.62% **only** to your shoulders and upper arms that will be covered by a short sleeve t-shirt.
 - Wash your hands **right away** with soap and water after applying ANDROGEL 1.62%.
 - After the gel has dried, **cover the application area with clothing**. Keep the area covered until you have washed the application area well or have showered.
 - **If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.**
 - **If a woman or child makes contact with the ANDROGEL 1.62% application area, that area on the woman or child should be washed well with soap and water right away.**

What is ANDROGEL 1.62%?

ANDROGEL 1.62% is a prescription medicine that contains testosterone. ANDROGEL 1.62% is used to treat adult males who have low or no testosterone.

Your healthcare provider will test your blood before you start and while you are taking ANDROGEL 1.62%.

It is not known if ANDROGEL 1.62% is safe or effective in children younger than 18 years old. Improper use of ANDROGEL 1.62% may affect bone growth in children.

ANDROGEL 1.62% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your ANDROGEL 1.62% in a safe place to protect it. Never give your ANDROGEL 1.62% to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

ANDROGEL 1.62% is not meant for use in women.

Who should not use ANDROGEL 1.62%?

Do not use ANDROGEL 1.62% if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breast-feeding. ANDROGEL 1.62% may harm your unborn or breast-feeding baby.

Women who are pregnant or who may become pregnant should avoid contact with the area of skin where ANDROGEL 1.62% has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using ANDROGEL 1.62%?

Before you use ANDROGEL 1.62%, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have kidney or liver problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using ANDROGEL 1.62% with certain other medicines can affect each other.

Especially, tell your healthcare provider if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of all of your medicines, if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use ANDROGEL 1.62%?

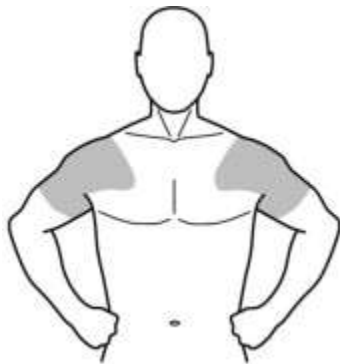
- It is important that you apply ANDROGEL 1.62% exactly as your healthcare provider tells you to.

- Your healthcare provider will tell you how much ANDROGEL 1.62% to apply and when to apply it.
- Your healthcare provider may change your ANDROGEL 1.62% dose. **Do not** change your ANDROGEL 1.62% dose without talking to your healthcare provider.
- **ANDROGEL 1.62% is to be applied to the area of your shoulders and upper arms that will be covered by a short sleeve t-shirt. Do not** apply ANDROGEL 1.62% to any other parts of your body such as your stomach area (abdomen), penis, or scrotum.
- Apply ANDROGEL 1.62% at the same time each morning. ANDROGEL 1.62% should be applied after showering or bathing.
- **Wash your hands right away** with soap and water after applying ANDROGEL 1.62%.
- Avoid showering, swimming or bathing for at least 2 hours after you apply ANDROGEL 1.62%.
- ANDROGEL 1.62% is flammable until dry. Let ANDROGEL 1.62% dry before smoking or going near an open flame.
- Let the application site dry completely before putting on a t-shirt.

Applying ANDROGEL 1.62%:

ANDROGEL 1.62% comes in a pump or in packets.

- **Before applying ANDROGEL 1.62% make sure that your shoulders and upper arms are clean, dry, and that there is no broken skin.**
- The application sites for ANDROGEL 1.62% are the upper arms and shoulders that will be covered by a short sleeve t-shirt (See Figure A).



(Figure A)

If you are using ANDROGEL 1.62% pump:

- Before using a new bottle of ANDROGEL 1.62 % for the first time, you will need to prime the pump. To prime the ANDROGEL 1.62% pump, slowly push the pump all the way down 3 times. **Do not** use any ANDROGEL 1.62% that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your ANDROGEL 1.62% pump is now ready to use.
- Remove the cap from the pump. Then, position the nozzle over the palm of your hand and slowly push the pump all the way down. Apply ANDROGEL 1.62% to the application site. You may also apply ANDROGEL 1.62% directly to the application site.

- **Wash your hands with soap and water right away.**

Find Your Dose as Prescribed by Your Healthcare Provider		Application Method
1 PUMP DEPRESSION	20.25 mg	Apply 1 pump depression of ANDROGEL 1.62% to 1 upper arm and shoulder.
2 PUMP DEPRESSIONS	40.5 mg	Apply 1 pump depression of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 1 pump depression of ANDROGEL 1.62% to the opposite upper arm and shoulder.
3 PUMP DEPRESSIONS	60.75 mg	Apply 2 pump depressions of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 1 pump depression of ANDROGEL 1.62% to the opposite upper arm and shoulder.
4 PUMP DEPRESSIONS	81 mg	Apply 2 pump depressions of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply 2 pump depressions of ANDROGEL 1.62% to the opposite upper arm and shoulder.

If you are using ANDROGEL 1.62% packets:

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the ANDROGEL 1.62% out of the packet into the palm of your hand. Apply ANDROGEL 1.62% to the application site. You may also apply ANDROGEL 1.62% directly to the application site.
- ANDROGEL 1.62% should be applied right away.
- **Wash your hands with soap and water right away.**

Find Your Dose as Prescribed by Your Healthcare Provider		Application Method
One 20.25 mg packet	20.25 mg	Apply 1 packet of ANDROGEL 1.62% to 1 upper arm and shoulder.
One 40.5 mg packet	40.5 mg	Apply half of the 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply the remaining packet contents to the opposite upper arm and shoulder.
One 40.5 mg packet and one 20.25 mg packet	60.75 mg	Apply one 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply one 20.25 mg packet of ANDROGEL 1.62% to the opposite upper arm and shoulder.
Two 40.5 mg packets	81 mg	Apply one 40.5 mg packet of ANDROGEL 1.62% to 1 upper arm and shoulder and then apply one 40.5 mg packet of ANDROGEL 1.62% to the opposite upper arm and shoulder.

What are the possible side effects of ANDROGEL 1.62%?

See **“What is the most important information I should know about ANDROGEL 1.62%?”**

ANDROGEL 1.62% can cause serious side effects including:

- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using ANDROGEL 1.62%.** This can include:
 - increased urination at night
 - trouble starting your urine stream
 - having to pass urine many times during the day
 - having an urge that you have to go to the bathroom right away
 - having a urine accident
 - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use ANDROGEL 1.62%.
- **In large doses ANDROGEL 1.62% may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling, or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of ANDROGEL 1.62% include:

- increased prostate specific antigen (a test used to screen for prostate cancer)
- mood swings
- hypertension
- increased red blood cell count
- skin irritation where ANDROGEL 1.62% is applied

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ANDROGEL 1.62%. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ANDROGEL 1.62%?

- Store ANDROGEL 1.62% at 59°F to 86°F (15°C to 30°C).

- When it is time to throw away the pump or packets, safely throw away used ANDROGEL 1.62% in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep ANDROGEL 1.62% away from fire.

Keep ANDROGEL 1.62% and all medicines out of the reach of children.

General information about the safe and effective use of ANDROGEL 1.62%

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ANDROGEL 1.62% for a condition for which it was not prescribed. Do not give ANDROGEL 1.62% to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ANDROGEL 1.62%. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ANDROGEL 1.62% that is written for health professionals.

For more information, go to www.androgel.com or call 1-800-633-9110.

What are the ingredients in ANDROGEL 1.62%?

Active ingredient: testosterone

Inactive ingredients: carbopol 980, ethyl alcohol, isopropyl myristate, purified water and sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA

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A090630057538-Revised June, 2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AXIRON safely and effectively. See full prescribing information for AXIRON.

AXIRON (testosterone) topical solution, for topical use CIII

Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning.

- Virilization has been reported in children who were secondarily exposed to topical testosterone products (5.2)
- Children should avoid contact with unwashed or unclothed application sites in men using AXIRON (2.2, 5.2)
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17)

RECENT MAJOR CHANGES

Warnings and Precautions, Venous Thromboembolism (5.4) 06/2014

INDICATIONS AND USAGE

AXIRON® is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Important limitations of use: Safety and efficacy of AXIRON in males <18 years old have not been established (8.4)

DOSAGE AND ADMINISTRATION

- Starting AXIRON dose is 60 mg of testosterone (1 pump actuation of 30 mg of testosterone to each axilla), applied once daily, at the same time each morning. (2.1)
- Apply to clean, dry intact skin of the axilla, not to any other parts of the body including the abdomen or genitals (2.2)
- Dose adjustment: The dose of testosterone may be decreased from 60 mg (2 pump actuations) to 30 mg (1 pump actuation) or increased from 60 mg to 90 mg (3 pump actuations) or from 90 mg to 120 mg (4 pump actuations) based on the serum testosterone concentration from a single blood draw 2 – 8 hours after applying AXIRON and at least 14 days after starting treatment or following dose adjustment. (2.2)
- Patients should wash hands immediately with soap and water after applying AXIRON and cover the application site with clothing after the solution has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)
- The application site and dose of AXIRON are not interchangeable with other topical testosterone products. (2.1)

DOSAGE FORMS AND STRENGTHS

AXIRON (testosterone) topical solution is available as a metered-dose pump. One pump actuation delivers 30 mg of testosterone. Each metered-dose pump is supplied with an applicator. (3)

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate (4, 5.1)
- Pregnant or breastfeeding women. Testosterone may cause fetal harm (4, 8.1, 8.3)

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AXIRON. Secondary exposure to testosterone can produce signs of virilization. AXIRON should be discontinued until the cause of the virilization is identified (2.2, 5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Exogenous administration of testosterone may lead to azoospermia (5.6)
- Edema with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.8).
- Sleep apnea may occur in those with risk factors (5.10)
- Monitor serum testosterone, prostate specific antigen (PSA), liver function, lipid concentrations, hematocrit and hemoglobin periodically (5.1, 5.3, 5.7, 5.11)
- AXIRON is flammable until dry (5.14)

ADVERSE REACTIONS

Most common adverse reactions (incidence >4%) are skin application site reactions, increased hematocrit, headache, diarrhea, vomiting, and increased serum PSA (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Androgens may decrease blood glucose and insulin requirement in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended (7.2).
- Use of testosterone with Adrenocorticotropic Hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).

USE IN SPECIFIC POPULATIONS

- There are insufficient long-term safety data in geriatric patients using AXIRON to assess the potential risks of cardiovascular disease and prostate cancer (8.5).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 06/2014

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- Virilization has been reported in children who were secondarily exposed to topical testosterone products [see *Warnings and Precautions* (5.2)].
- Children should avoid contact with unwashed or unclothed application sites in men using AXIRON [see *Dosage and Administration* (2.2) and *Warnings and Precautions* (5.2)].
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.2) and *Patient Counseling Information* (17)].

1 INDICATIONS AND USAGE

AXIRON is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Important limitations of use — Safety and efficacy of AXIRON in males <18 years old have not been established [see *Use in Specific Populations* (8.4)].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose of AXIRON (testosterone) topical solution is 60 mg of testosterone (2 pump actuations) applied once daily.

To ensure proper dosing, serum testosterone concentrations should be measured after initiation of therapy to ensure that the desired concentrations (300 ng/dL–1050 ng/dL) are achieved. The AXIRON dose can be adjusted based on the serum testosterone concentration from a single blood draw 2 – 8 hours after applying AXIRON and at least 14 days after starting treatment or following dose adjustment.

If the measured serum testosterone concentration is below 300 ng/dL, the daily testosterone dose may be increased from 60 mg (2 pump actuations) to 90 mg (3 pump actuations) or from 90 mg to 120 mg (4 pump actuations). If the serum testosterone concentration exceeds 1050 ng/dL, the daily testosterone dose should be decreased from 60 mg (2 pump actuations) to 30 mg (1 pump actuation) as instructed by a physician. If the serum testosterone concentration consistently exceeds 1050 ng/dL at the lowest daily dose of 30 mg (1 pump actuation), AXIRON therapy should be discontinued.

The application site and dose of AXIRON are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AXIRON is applied to the axilla, preferably at the same time each morning, to clean, dry, intact skin. Do not apply AXIRON to other parts of the body including to the scrotum, penis, abdomen, shoulders or upper arms. After applying the solution, the application site should be allowed to dry completely prior to dressing. Avoid fire, flames or smoking until the solution has dried since alcohol based products, including AXIRON, are flammable.

AXIRON is applied to the axilla using an applicator. When using AXIRON for the first time, patients should be instructed to prime the pump by depressing the pump three (3) times, discard any product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly. This priming should be done only prior to the first use of each pump. After priming, patients should completely depress the pump one time (one pump actuation) to dispense 30 mg of testosterone. To dispense the solution, position the nozzle over the applicator cup and carefully depress the pump fully once. Ensure that the liquid is directed into the cup. The cup should be filled with no more than 30 mg (1 pump actuation) of testosterone. Dosing that requires greater than one pump actuation must be applied in increments of 30 mg as is shown in Table 1.

Keeping the applicator upright, patients should place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, it can be wiped back up with the applicator cup. The solution should not be rubbed into the skin with fingers or hand. The process is then repeated with application of 30 mg of testosterone (1 pump actuation) to the other axilla to achieve a total of 60 mg of testosterone applied. For patients prescribed the 90 mg dose of testosterone, the procedure is the same, but three applications are required. To dose 120 mg of testosterone, four applications are required alternating left and right for each application as shown in Table 1. When repeat application to the same axilla is required, the axilla should be allowed to dry completely before more AXIRON is applied.

After use, the applicator should be rinsed under room temperature, running water and then patted dry with a tissue. The applicator and cap are then replaced on the bottle for storage.

When deodorants or antiperspirants are used as part of a regular program for personal hygiene, they should not interfere with the efficacy of AXIRON in treating hypogonadism. If patients use an antiperspirant or deodorant (stick or roll-on) then it should be applied prior to the application of AXIRON to avoid contamination of the stick or roll-on product.

Patients should be advised to avoid swimming or washing the application site until two hours following application of AXIRON [see *Clinical Pharmacology* (12.3)].

To reduce the likelihood of interpersonal transfer of testosterone, the application site should always be washed prior to any skin-to-skin contact regardless of the length of time since application. [See *Warnings and Precautions* (5.2)].

Table 1: Application Technique

Daily Prescribed Dose of Testosterone	Number of Pump Actuations	Application
30 mg	1 (once daily)	Apply once to one axilla only (left OR right)
60 mg	2 (once daily)	Apply once to the left axilla and then apply once to the right axilla.
90 mg	3 (once daily)	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply once again to the left OR right axilla.
120 mg	4 (once daily)	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply once again to the left AND once to the right axilla.

Hands should be washed thoroughly with soap and water after AXIRON has been applied [see *Warnings and Precautions* (5.2)].

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AXIRON treated skin:

- Children and women should avoid contact with the unclothed or unwashed application sites on the skin of men using AXIRON.
- Patients should wash their hands immediately with soap and water after application of AXIRON.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the solution has dried.
- Prior to any situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AXIRON has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

While interpersonal testosterone transfer can occur with a T-shirt on, it has been shown that transfer can be substantially reduced by wearing a T-shirt and the majority of residual testosterone is removed from the skin surface by washing with soap and water.

3 DOSAGE FORMS AND STRENGTHS

AXIRON is a (testosterone) topical solution available as a metered-dose pump. One pump actuation delivers 30 mg of testosterone. Each metered-dose pump is supplied with an applicator.

4 CONTRAINDICATIONS

- AXIRON is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate [see *Warnings and Precaution* (5.1)].
- AXIRON is contraindicated in women who are, or who may become pregnant, or who are breastfeeding. AXIRON may cause fetal harm when administered to a pregnant woman. AXIRON may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to AXIRON, she should be apprised of the potential hazard to the fetus. [See *Use in Specific Populations* (8.1, 8.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH.
- Patients treated with Androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It would be appropriate to reevaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices. [See *Contraindications* (4)].

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen or upper arms, including cases of secondary exposure resulting in virilization of children. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with

removal of the exposure to testosterone. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AXIRON [see *Dosage and Administration* (2.2), *Use in Specific Populations* (8.1) and *Clinical Pharmacology* (12.3)].

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone should also be brought to the attention of a physician. Testosterone therapy should be promptly discontinued at least until the cause of virilization has been identified. [See *Dosage and Administration* (2.2)].

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as AXIRON. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AXIRON and initiate appropriate workup and management [see *Adverse Reactions* (6.2)].

5.5 Use in Women

Due to lack of controlled studies in women and potential virilizing effects, AXIRON is not indicated for use in women [see *Contraindications* (4) and *Use in Specific Populations* (8.1, 8.3)].

5.6 Potential for Adverse Effects on Spermatogenesis

At large doses of exogenous androgens, including AXIRON, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

5.7 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AXIRON is not known to cause these adverse effects.

5.8 Edema

Androgens, including AXIRON, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease [see *Adverse Reactions* (6)].

5.9 Gynecomastia

Gynecomastia may develop and may persist in patients being treated with androgens, including AXIRON, for hypogonadism.

5.10 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity and chronic lung disease.

5.11 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.12 Hypercalcemia

Androgens, including AXIRON, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.13 Decreased Thyroxine-binding Globulin

Androgens, including AXIRON, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentration and increased resin uptake of T3 and T4. Free thyroid hormone concentration remain unchanged, however there is no clinical evidence of thyroid dysfunction.

5.14 Flammability

Alcohol based products, including AXIRON, are flammable; therefore, patients should be advised to avoid smoking, fire or flame until the AXIRON dose applied has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Hypogonadal Men

Table 2 shows the treatment emergent adverse reactions that were reported by either >4% of 155 patients in a 120 day, Phase 3 study or by >4% of 71 patients who continued to use AXIRON for up to 180 days. These data reflect the experience primarily with a testosterone dose of 60 mg, which was taken by all patients at the start of the study, and was the maintenance dose for 97 patients. However, the doses used varied from 30 mg to 120 mg.

Table 2: Adverse Reactions Seen With the Use of AXIRON in either the 120 Day Clinical Trial or in the Extension to 180 Days (>4%)

Event	120 Days (155 Patients)	180 Days (71 Patients)
Application Site Irritation	11 (7%)	6 (8%)
Application Site Erythema	8 (5%)	5 (7%)
Headache	8 (5%)	4 (6%)
Hematocrit Increased	6 (4%)	5 (7%)
Diarrhea	4 (3%)	3 (4%)
Vomiting	4 (3%)	3 (4%)
PSA Increased	2 (1%)	3 (4%)

Other less common adverse reactions reported by at least 2 patients in the 120 day trial included: application site edema, application site warmth, increased hemoglobin, hypertension, erythema (general), increased blood glucose, acne, nasopharyngitis, anger and anxiety. Other less common adverse reactions reported in fewer than 1% of patients in the 120 day trial included: asthenia, affect lability, folliculitis, increased lacrimation, breast tenderness, increased blood pressure, increased blood testosterone, neoplasm prostate and elevated red blood cell count.

During the 120 day trial one patient discontinued treatment because of affect lability/anger which was considered possibly related to AXIRON administration.

During the 120 day clinical trial there was an increase in mean PSA values of 0.13 ± 0.68 ng/mL from baseline. At the end of the 180 day extension clinical trial, there was an overall increase in mean PSA values of 0.1 ± 0.54 ng/mL.

Following the 120 day study, seventy-one (71) patients entered a two-month extension study with AXIRON. Two patients (3%) had adverse reactions that led to discontinuation of treatment during the period from Day 120 to Day 180. These reactions were: one patient with application site irritation (considered possibly related to AXIRON application) and one patient with dry skin and erythema, but not at the application site (considered not related to AXIRON administration) and application site erythema (considered possibly related to AXIRON administration).

No serious adverse reactions to AXIRON were reported during either the 120 day trial, or the extension to 180 days.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AXIRON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Vascular Disorders: Venous thromboembolism [see *Warnings and Precautions* (5.4)].

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.

7.2 Oral anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications* (4)] — AXIRON is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AXIRON is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation. [See *Contraindications* (4)].

8.4 Pediatric Use

Safety and efficacy of AXIRON has not been established in males <18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AXIRON to determine whether efficacy in those over 65 years of age differs from younger patients. Of the 155 patients enrolled in the pivotal clinical study utilizing AXIRON, 21 were over 65 years of age. Additionally, there were insufficient long-term safety data in these patients utilizing AXIRON to assess a potential incremental risk of cardiovascular disease and prostate cancer.

8.6 Renal Impairment

No formal studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No formal studies were conducted involving patients with hepatic impairment.

8.8 Use in Men with Body Mass Index (BMI) >35 kg/m²

Safety and efficacy of AXIRON in males with BMI >35 kg/m² has not been established.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AXIRON contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

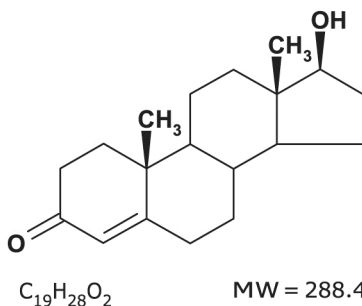
- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drug are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

No cases of overdose with AXIRON have been reported in clinical trials. There is one report of acute overdose by injection of testosterone enanthate: testosterone concentrations of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdose would consist of discontinuation of AXIRON together with appropriate symptomatic and supportive care.

11 DESCRIPTION

AXIRON (testosterone) topical solution is a clear, colorless, single phase solution containing 30 mg of testosterone in 1.5 mL of AXIRON solution for topical administration through the axilla. The active pharmacologic ingredient in AXIRON is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



The inactive ingredients are ethanol, isopropyl alcohol, octisalate, and povidone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AXIRON.

12.3 Pharmacokinetics

Absorption — AXIRON delivers physiologic circulating testosterone that approximate normal concentration range (i.e., 300 - 1050 ng/dL) seen in healthy men following application to the axilla.

On the skin, the ethanol and isopropyl alcohol evaporate leaving testosterone and octisalate. The skin acts as a reservoir from which testosterone is released into the systemic circulation over time (see Figure 1). In general, steady-state serum concentrations are achieved by approximately 14 days of daily dosing.

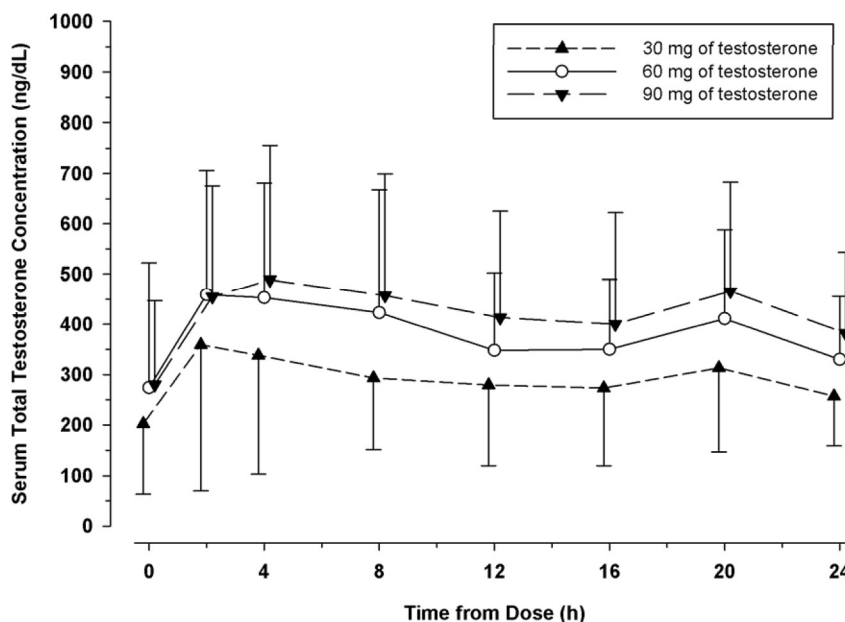


Figure 1: Mean (±SD) Serum Testosterone Concentrations on Day 7 in Patients Following AXIRON Once-Daily Application of 30 mg, 60 mg, or 90 mg of Testosterone

When AXIRON treatment is discontinued after achieving steady-state, serum testosterone concentrations returned to their pretreatment concentrations by 7 – 10 days after the last application.

Distribution — Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism — Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).

DHT concentration increased in parallel with testosterone concentration during AXIRON treatment. The mean steady-state DHT/T ratio remained within normal limits and ranged from 0.17 to 0.26 across all doses on Days 15, 60, and 120.

Excretion — There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Potential for testosterone transfer: The potential for testosterone transfer from males dosed with AXIRON to healthy females was evaluated in a clinical study conducted with a 2% testosterone formulation. 10 males were treated with 60 mg (2 pump actuations) of testosterone in each axilla (the maximum testosterone dose of 120 mg). At 2 hours after the application of AXIRON to the males, the females rubbed their outer forearms for 15 minutes on the axilla of the males. The males had covered the application area with a T-shirt. Serum concentrations of testosterone were monitored in the female subjects for 72 hours after the transfer procedure. Study results show a 13% and 17% increase in testosterone exposure ($AUC_{[0-24]}$) and maximum testosterone concentration (C_{max}), respectively, compared to baseline in these females. In a prior clinical study conducted with a 1% testosterone formulation under similar study conditions, direct skin-to-skin transfer showed a 131% and 297% increase in testosterone exposure ($AUC_{[0-72]}$) and maximum testosterone concentration (C_{max}), respectively, compared to when men had covered the application area with a T-shirt.

In a clinical study conducted with a 2% testosterone formulation to evaluate the effect of washing on the residual amount of testosterone at the axilla, 10 healthy male subjects received 60 mg (2 pump actuations) of testosterone to each axilla (the maximum testosterone dose of 120 mg). Following 5 minutes of drying time, the left axilla was wiped with alcohol towelettes which were assayed for testosterone content. Subjects were required to shower with soap and water 30 minutes after application. The right axilla was then wiped with alcohol towelettes which were assayed for testosterone content. A mean (SD) of 3.1 (2.8) mg of residual testosterone (i.e., 92.6% reduction compared to when axilla was not washed) was recovered after washing this area with soap and water. [See *Dosage and Administration (2.2)* and *Warnings and Precautions (5.2)*].

Use of deodorants and anti-perspirants: In a parallel designed clinical study evaluating the effect of deodorants and antiperspirants in healthy premenopausal females dosed with AXIRON, each subject applied either a combined deodorant/antiperspirant spray (6 subjects) or stick (6 subjects) or a deodorant spray (6 subjects) to a single axilla 2 minutes before the application of 30 mg (1 pump actuation) of testosterone to the same axilla. A control group of 6 subjects only applied 30 mg (1 pump actuation) of testosterone to a single axilla. Blood samples were collected for 72 hours from all subjects following AXIRON administration. Although a decrease of up to 33% of testosterone exposure ($AUC_{[0-72]}$) was observed when antiperspirants or deodorants are used 2 minutes prior to AXIRON application, underarm deodorant or antiperspirant spray or stick products may be used 2 minutes prior to AXIRON application as part of normal, consistent, and daily routine. [See *Dosage and Administration (2.2)*, and *Patient Counseling Information (17.4)*].

Effect of showering/washing: In a parallel designed clinical study to evaluate the effect of washing on the testosterone systemic exposure, two groups of 6 healthy premenopausal female subjects were each dosed with 30 mg (1 pump actuation) of testosterone to a single axilla. The application sites of each group were washed with soap and water 2 hours or 6 hours after the application of AXIRON. A control group of 6 female subjects applied 30 mg (1 pump actuation) of testosterone to a single axilla and did not wash the application site. Blood samples were collected for 72 hours from all subjects following dosing with AXIRON. A decrease of up to 35% of testosterone exposure ($AUC_{[0-72]}$) was observed when applications sites were washed 2 hours and 6 hours after AXIRON application. Patients should be advised to avoid swimming or washing the application site until 2 hours following application of AXIRON. [See *Dosage and Administration (2.2)* and *Patient Counseling Information (17.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Studies in Hypogonadal Men

AXIRON was evaluated in a multicenter, open label, 120-day trial that enrolled 155 hypogonadal men at 26 clinical research centers. The median age of subjects was 53 years with a range of 19 – 78 years. Of the 144 subjects whose race was recorded, 122 (84.7%) were Caucasian, 13 (9.0%) were Hispanic, 6 (4.2%) were African Americans, 1 (0.7%) was Asian and 2 (1.4%) had race recorded as “Other”.

Patients were instructed to apply AXIRON to unclothed, clean, dry, and unbroken skin. The solution was applied to the axillary area. Patients were not instructed to alter their normal grooming routine, e.g., shave under the arm.

During the initial AXIRON treatment period (Days 1-15) 143 patients were treated with 60 mg of testosterone daily. On Day 45 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their 24 hour average serum testosterone concentration measured on Day 15. On Day 90 of the trial, patients were maintained at the same dose, or were titrated up or down, based on their 24 hour average serum testosterone concentration measured on Day 60.

On day 120, 75% of responding patients finished the study on the starting dose of 60 mg of testosterone, while 2% had been titrated to 30 mg, 17% had been titrated to 90 mg and 6% had been titrated to the 120 mg dose.

On day 60, 84.8% of subjects had total testosterone concentrations in the normal range. Of those who had sufficient data for analysis on day 120, 84.1%, had their average serum testosterone concentration in the normal range of 300 – 1050 ng/dL.

Table 3 summarizes the proportion of subjects having average testosterone concentrations within the normal range on Days 60 and 120.

Table 3: Proportion of subjects who had an average Serum Total Testosterone in the range 300 to 1050 ng/dL and completed 120 days of treatment (N=138^a)

Evaluation Time	Statistics	Value
Baseline Testosterone	Mean (SD)	194.6 ng/dL (92.9 ng/dL)
Day 15	Normal ^b	76.1% ^c
	95% CI	(69.0%, 83.2%)
Day 60	Normal ^b	84.8%
	95% CI	(78.8%, 90.8%)
Day 120	Normal ^b	84.1%
	95% CI	(77.9%, 90.2%)

^a Three patients who withdrew from the study due to adverse reactions are included as treatment failures.

^b Normal represents the percentage of patients with average testosterone concentration in the range of 300 – 1050 ng/dL.

^c On Day 15, 72.2% of the 90 subjects in the US study population had an average serum testosterone in the range of 300 ng/dL – 1050 ng/dL.

Of the 135 patients who completed the 120 day treatment, 123 patients did so with no deviation from the protocol. By day 120, average serum testosterone concentration was within normal range for 67% of those who titrated down on the 30 mg dose, 89% of those on the 60 mg dose, 86% of those who titrated up to 90 mg and 70% of those who titrated up to the 120 mg dose. Table 4 below summarizes the testosterone concentration data in the patients who completed 120 days.

Table 4: Baseline-unadjusted Arithmetic Mean (±SD) Steady-State Serum Testosterone Concentrations on Days 15, 60 and 120 in Patients Who Completed 120 Days of Treatment

	Dose of AXIRON				Overall
	30 mg	60 mg	90 mg	120 mg	
Day 15	[N=0]	[N=135]	[N=0]	[N=0]	[N=135]
C _{avg} (ng/dL)	--	456 (±226)	--	--	456 (±226)
C _{max} (ng/dL)	--	744 (±502)	--	--	744 (±502)
Day 60	[N=1]	[N=105]	[N=29]	[N=0]	[N=135]
C _{avg} (ng/dL)	343 (--)	523 (±207)	368 (±138)	--	488 (±204)
C _{max} (ng/dL)	491 (--)	898 (±664)	646 (±382)	--	840 (±620)
Day 120	[N=3]	[N=97]	[N=25]	[N=10]	[N=135]
C _{avg} (ng/dL)	493 (±239)	506 (±175)	415 (±165)	390 (±160)	480 (±177)
C _{max} (ng/dL)	779 (±416)	839 (±436)	664 (±336)	658 (±353)	792 (±417)

Figure 2 summarizes the pharmacokinetic profiles of total testosterone in patients completing 120 days of AXIRON treatment administered as 60 mg of testosterone for the initial 15 days followed by possible titration according to follow-up testosterone measurements.

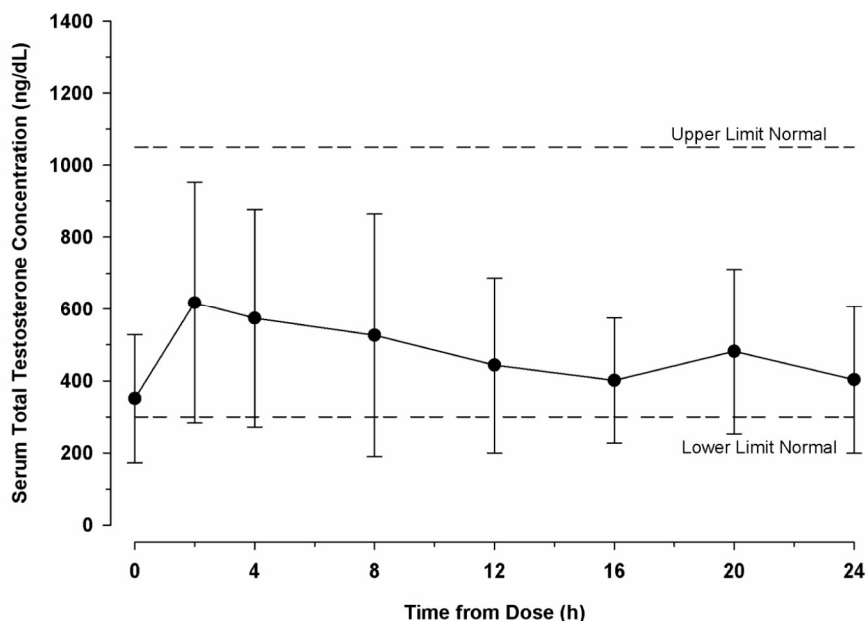


Figure 2: Mean (\pm SD) Steady-State Serum Testosterone Concentrations on Day 120 (30, 60, 90 or 120 mg testosterone) in Patients Who Completed 120 Days (N=135) of AXIRON Once-Daily Treatment

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AXIRON (testosterone) topical solution is available as a metered-dose pump containing 110 mL of solution. The pump is capable of dispensing 90 mL of solution in 60 metered pump actuations. One pump actuation delivers 30 mg of testosterone in 1.5 mL of solution. Each metered-dose pump is supplied with an applicator. Neither the bottle nor the applicator cup contains latex.

NDC 0002-1975-90

16.2 Storage and Handling

Keep AXIRON out of reach of children.

Store at 25°C (77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature.

Used AXIRON bottles and applicators should be discarded in household trash in a manner that prevents accidental exposure of children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide.

Patients should be informed of the following information:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use AXIRON. [See *Contraindications (4)* and *Warnings and Precaution (5.1)*].

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Cases of secondary exposure to testosterone in children and women have been reported with topical testosterone products applied to the abdomen, shoulders or upper arms, including cases of secondary exposure resulting in virilization of children, with signs and symptoms including enlargement of the penis or clitoris, premature development of pubic hair, increased erections, aggressive behavior and advanced bone age. Inappropriate changes in genital size or premature development of pubic hair or libido in children, or changes in hair distribution, increase in acne, or other signs of testosterone effects in adult women should be brought to the attention of a physician and the possibility of secondary exposure to AXIRON also should be brought to the attention of a physician. AXIRON should be promptly discontinued at least until the cause of virilization is identified.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AXIRON treated skin:

- AXIRON should only be applied to the axilla, not to any other part of the body.

- Children and women should avoid contact with the unwashed skin of the axilla or unclothed application sites of men where AXIRON has been applied.
- Patients should wash their hands immediately with soap and water after application of AXIRON.
- Patients should cover the axilla application site(s) with clothing (e.g., a shirt) after waiting 3 minutes for the solution to dry.
- Prior to any situation in which direct skin-to-skin contact of the axilla is anticipated, patients should wash the axilla to which AXIRON has been applied thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AXIRON has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

[See Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with Androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having urine accident, being unable to pass urine and having a weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should be Advised of these Application Instructions

- The pump should be primed by depressing it 3 times prior to its first use. No priming is needed with subsequent uses of that pump.
- AXIRON should NOT be applied to the scrotum, penis, abdomen, shoulders or upper arms.
- With testosterone doses greater than 60 mg, which require two applications of AXIRON to the same axilla, the product should be allowed to dry after the first application before the second is applied.
- AXIRON should be applied once daily at approximately the same time each day. AXIRON should be applied to clean, dry skin.
- Patients may use an antiperspirant or deodorant spray before applying AXIRON. If patients use a stick or roll-on antiperspirant or deodorant, then it should be applied prior to application of AXIRON to avoid contamination of the stick or roll-on product.
- Avoid swimming or washing the application site until two hours following application of AXIRON *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.
- Avoid splashing in the eyes. In case of contact with eyes, flush thoroughly with water. If irritation persists, seek medical advice.

Literature revised JUN 2014

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Medication Guide

AXIRON[®] (AXE-e-RON) CIII (testosterone) topical solution

Read this Medication Guide before you start using AXIRON and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AXIRON?

AXIRON can transfer from your body to others. This can happen if other people come into contact with the area where the AXIRON was applied.

Signs of puberty that are not expected (for example, pubic hair) have happened in young children who were accidentally exposed to testosterone through skin to skin contact with men using topical testosterone products like AXIRON.

- **Women and children should avoid contact with the unwashed or unclothed area where AXIRON has been applied. If a woman or child makes contact with the application area, the contact area on the woman or child should be washed well with soap and water right away.**
- To lower the risk of transfer of AXIRON from your body to others, you should follow these important instructions:
 - Apply AXIRON **only** to your armpits.
 - Wash your hands **right away** with soap and water after applying AXIRON.
 - After the solution has dried, **cover the application area with clothing**. Keep the area covered until you have washed the application area well or have showered.
 - **If you expect another person to have direct skin-to-skin contact with your armpits, first wash the application area well with soap and water.**

Stop using AXIRON and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to AXIRON:

Signs and symptoms in **children** may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive
- aggressive behavior

Signs and symptoms in **women** may include:

- changes in body hair
- a large increase in acne

What is AXIRON?

AXIRON is a prescription medicine that contains testosterone. AXIRON is used to treat adult males who have low or no testosterone.

Your healthcare provider will test your blood before you start and while you are taking AXIRON.

It is not known if AXIRON is safe and effective in children younger than 18 years old. Improper use of AXIRON may affect bone growth in children.

AXIRON is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your AXIRON in a safe place to protect it. Never give AXIRON to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and it is against the law.

AXIRON is not meant for use in women.

Who should not use AXIRON?

Do not use AXIRON if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breast-feeding. AXIRON may harm your unborn or breast-feeding baby.

Women who are pregnant or who may become pregnant should avoid contact with the area of skin where AXIRON has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using AXIRON?

Before you use AXIRON, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have kidney or liver problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using AXIRON with other medicines can affect each other.

Especially tell your healthcare provider if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of all of your medicines if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use AXIRON?

- It is important that you apply AXIRON exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much AXIRON to apply and when to apply it.

- Your healthcare provider may change your AXIRON dose. Do not change your AXIRON dose without talking to your healthcare provider.
- **AXIRON is to be applied to the armpits only.** Do not apply AXIRON to any other parts of your body such as your stomach area (abdomen), penis, scrotum, shoulders or upper arms.
- Do not apply AXIRON with your fingers or hands.
- Apply AXIRON at about the same time each morning. AXIRON should be applied after showering or bathing.
- Avoid swimming or bathing for at least 2 hours after you apply AXIRON.
- You can use an antiperspirant or deodorant before applying AXIRON. If you use antiperspirant or deodorant, then it should be applied at least 2 minutes before you apply AXIRON.
- **AXIRON is flammable until dry. Let AXIRON dry before smoking or going near an open flame.**
- **Avoid splashing in the eyes. In case of contact with eyes, flush thoroughly with water. If irritation persists, seek medical advice.**

Applying Axiron



AXIRON

Figure 1

- Before using a new bottle of AXIRON for the first time, you will need to prime the pump. To prime the AXIRON pump gently push down on the pump 3 times. Do not use any AXIRON that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your AXIRON pump is now ready to use.
- **Use AXIRON exactly as your healthcare provider tells you to use it.** Your healthcare provider will tell you the dose of AXIRON that is right for you. Apply your dose correctly by following the application instructions in the table below.

Find Your Dose as Prescribed by Your Doctor	Each application equals 1 depression of the pump.
30 mg	Apply 1 application once to one armpit only (left OR right).
60 mg	Apply 2 applications: one to the left armpit and then one to the right armpit.
90 mg	Apply 3 applications: one to the left and one to the right armpit, wait for the product to dry, and then apply again one to the left OR right armpit.
120 mg	Apply 4 applications: one to the left and one to the right armpit, wait for the product to dry, and then apply again one to the left AND one to the right armpit.

- Before applying AXIRON, make sure that your armpit is clean, dry and that there is no broken skin.



Figure 2

- Remove the cap and the applicator cup from the pump. Then, position the nozzle over the applicator cup and depress the pump gently (see Figure 2).



Figure 3

- To apply the AXIRON solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up (see Figure 3).
- If AXIRON drips or runs, wipe it back up with the applicator cup. Do not rub in the solution with your fingers or hand once it has been applied.

- Let the application site dry completely before putting on a shirt.
- After you have finished applying AXIRON, rinse the applicator cup with room temperature running water, and then pat it dry with a tissue. Carefully replace the applicator cup and cap back onto the bottle and make sure you store the bottle safely.
- Clean up any spilled solution from surfaces such as the sink or floor to make sure others do not come into contact with it.
- **Wash your hands with soap and water right away.**

What are the possible side effects of AXIRON?

See also “What is the most important information I should know about AXIRON?”

AXIRON can cause serious side effects including:

- If you already have enlargement of your prostate gland your signs and symptoms can get worse while using AXIRON. This can include:
 - increased urination at night
 - trouble starting your urine stream
 - having to pass urine many times during the day
 - having an urge that you have to go to the bathroom right away
 - having a urine accident
 - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use AXIRON.
- **In large doses AXIRON may lower your sperm count.**

- **Swelling of your ankles, feet, or body.**
- **Enlarged or painful breasts.**
- **Problems breathing while you sleep (sleep apnea).**
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of AXIRON include:

- skin redness or irritation where AXIRON is applied
- increased red blood cell count
- headache
- diarrhea
- vomiting
- increase in blood level of Prostate Specific Antigen (a test used to screen for prostate cancer)

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of AXIRON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AXIRON?

Store AXIRON at 15°C to 30°C (59°F to 86°F)

When it is time to throw away the bottle, safely throw away all parts of the AXIRON dispenser including bottle applicator cup and cap. Be careful to prevent accidental exposure of children or pets.

Keep AXIRON away from fire.

General information about AXIRON

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AXIRON for a condition for which it was not prescribed. Do not give AXIRON to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about AXIRON. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about AXIRON that is written for health professionals.

For more information, go to www.axiron.com or call 1-800-545-5979.

What are the ingredients in AXIRON?

Active ingredient: testosterone.

Inactive ingredients: ethanol, isopropyl alcohol, octisalate, and povidone.

The bottle or applicator cup does not contain latex.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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