

## Stakeholder Feedback and ODPRN's Response: Testosterone Replacement Therapies

### Consolidated Report

Pg. 12, "Overview of Findings" Section

- "Diagnosis of ...Complex", paragraph 1: A stakeholder agrees with the ODPRN that there needs to be a consensus in terms of diagnosis (i.e. what testosterone levels should be considered normal and which symptoms should be considered?) before any change in policy takes place. A stakeholder also agrees with the ODPRN that there is a need to re-define current OPDP limited use criteria, regardless of the kind of policy being implemented, in order to better align with current TRT clinical practice guidelines.

*RESPONSE: It is beyond the scope of the ODPRN Drug Class Review to provide consensus guidelines for the management of patients with hypogonadism. However, based on best-available evidence (through published sources as well as our own research), advice from our clinical experts, and recommendations from our Citizen's Panel, policy recommendations (including revision of limited use criteria) for the TRTs will be made to the OPDP. No changes to the report were made.*

- "Multiple Factors...choices", paragraph 2: The ODPRN states that a review of existing guidelines suggests that choice of the testosterone formulation should be based on numerous factors, including patient's preference, treatment burden and costs and should be made as a joint decision between patient and physician. A stakeholder agrees with the ODPRN's findings that physicians and patients should have access to the TRT of their choice. Therefore, a stakeholder questions why two of the three final ODPRN policy recommendations restrict access to certain TRT and therefore, restrict physician and patient choice and may increase the overall burden of treatment. Furthermore, topical formulations, like AndroGel, are restricted in 3 out of the 4 ODPRN policy recommendations despite their proven efficacy in head to head trials, patient preference, patient preference, improved adherence and confirmed diagnosis (i.e. laboratory test).

*RESPONSE: Choice of a testosterone formulation is guided by various factors including patient preference, treatment burden (e.g., visit to the physician's office to receive injectable), cost (if patient is self-paying) and adverse effects (e.g., local reactions from topical products). Each of the reimbursement options presented includes all formulations of testosterone (i.e., oral, injectable, topical), and thus allows patients and their physicians to have access to the testosterone of their choice.*

*Changes to the report (under Accessibility and utilization, page 25): Selection of a product is influenced by factors such as patient preference, treatment burden, cost and adverse effects.*

- A stakeholder believes that there is a fundamental gap between the existing clinical evidence from the meta-analyses and the ODPRN's final policy recommendations. Specifically,

AndroGel was shown to be statistically better in head to head trials in terms of achieving normal serum testosterone levels over a 3-month period whereas Andriol was significantly worse. Delatestryl was associated with fluctuations in testosterone levels, resulting in instability in mood, libido and sexual function and has higher rates of erythrocytosis, a potential serious condition. In this vein, although no cost-effectiveness studies exist to confirm value for money between TRT per se, basic health economic principles suggest that TRT which offer better efficacy should inherently offer more value for money than TRT where efficacy is inferior or sub-optimal over time. This is true when reviewing product recommendations from Canadian federal agencies, like the Common Drug Review, CADTH and the PMPRB, who all recognize that a product that shows superior efficacy versus comparators typically justifies a higher price versus products in the same therapeutic class that do not.

*RESPONSE: The recommendations are based on input from all research teams including the systematic review team, pharmacoeconomics team, qualitative team as well as the pharmacoepidemiology team. As stated, the systematic review team showed that AndroGel (as well as Delatestryl and other testosterone products) was associated with a substantive increase in serum testosterone. However, they were unable to evaluate the potential fluctuations with Delatestryl, nor were they able to evaluate erythrocytosis associated with the testosterone products. In addition, no differences in clinically important outcomes were noted, including quality of life measures, libido, erectile dysfunction or depression. It should be noted that the pharmacoepidemiology team demonstrated that there is an increase in utilization of TRT products, in particular the use of topical products in men 65 years and older. No changes were made to the report.*

- A stakeholder recommends that AndroGel, not be restricted access in Ontario due to its higher acquisition costs since it has a proven safety profile, is more efficacious than oral therapies and injectables and is preferred amongst OPDP beneficiaries aged 65 years and older compared to other TRT. The ODPRN's BIA does not present a balanced or accurate view of the costs that may be associated with comparator therapies, such as a lack of or sub-optimal efficacy, higher healthcare utilization costs and poorer treatment adherence and failures. As such, the inclusion of these other important costs in the BIA will likely off-set the higher acquisition cost of AndroGel, making it a cost-effective TRT for physicians, patients and the OPDP.

*RESPONSE: A formal cost-effectiveness model was not completed for this review due to the heterogeneous populations included for the review. In our systematic review, no differences were noted between the various TRT formulations in terms of safety issues, although it is noted that there was limited data available. From an efficacy standpoint, no differences were noted between TRT formulations for outcomes of quality of life, libido, erectile dysfunction or depression. Users of injectable TRT products had more physician office visits. No changes have been made to the BIA. However, a note has been added to the statement: "The monthly average cost per user for the topical products (excluding the patch and Axiron) is greater than either the injectable or oral products (\$115.80 vs. \$24.77 and \$65.16, respectively). Note that this represents drug costs only*

*and excludes other healthcare related costs (e.g., physician visit for administration of injectable TRT)."*

- Choice of treatment for TRT: injectable formulations are associated with wide-peak-to-trough fluctuations in serum testosterone levels which may lead to instability in mood, libido and sexual function and has higher rates of erythrocytosis, a potential serious condition. A stakeholder is concerned that the ODPRN would recommend that this formulation be preferred in any future policy decision (i.e. Options 3 and 4).

*RESPONSE: No significant differences among the various testosterone replacement therapies were found in our systematic review for quality of life, erectile dysfunction, libido or depression. As well, data on erythrocytosis were limited and poorly reported. In the qualitative interviews with patients, the most preferred products were the gel products and the injectables. Therefore, based on efficacy, safety and patient preference, the topical and injectable products are comparable. However, the monthly drug cost associated with the injectable products is less than the topical products; this cost factor is considered in the policy recommendations listing injectable TRT as Limited Use. No changes to the report were made.*

- **Consolidated Report, Pg. 4:** "However, concern has been raised regarding the rise in utilization of TRT products, in particular the use of topical products in men 65 years and older, despite no apparent increase in the prevalence of hypogonadal conditions for which TRT is approved"
  - **Comment(s):** Increased utilization of a drug class does need to be solely attributed to an increase in disease prevalence. Increased use of TRT products in particular may partly be due to patient dissatisfaction with alternative therapies. In the Qualitative Study Findings Report, oral formulations were documented to be burdensome because they have to be consumed with fats and perceived to be less efficacious. In addition, the Consolidated Report states that selection of a product is often influenced by factors such as patient preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and adverse effects. It should also be noted that the prevalence of hypogonadism does not seem well documented. Based on the Environment Scan Report, late-onset hypogonadism varies between 2 to 40%, depending on population studied and definition.

*RESPONSE: Sentence has been clarified to read: "However, concern has been raised regarding the risk in utilization of TRT products, in particular the use of topical products in men 65 years and older, despite no apparent increase in the prevalence of classic hypogonadal conditions (e.g., androgen deficiency due to disorders of the hypothalamic-pituitary-testicular axis) for which TRT is approved."*

- **Consolidated Report, Pg. 4:** "In Ontario, there may be as many as 80% of men currently using TRT who do not meet the Limited Use (LU) Criteria;..."
  - **Comment(s):** A range for the percentage of men not meeting the LU criteria should be

specified. Currently, the upper limit of 80% is only specified.

*RESPONSE: Sentence has been changed to read: "In Ontario, there may be as many as 40-80% of men currently using TRT who do not meet ..."*

- **Consolidated Report, Pg. 4-5:** "The monthly average cost per user for the topical products (not including Androderm, Androgel pump or Axiron) is greater than either the injectable or oral products (\$115.80 vs. \$24.77 and \$65.16, respectively.)"
  - **Comment(s):** The sentence should clarify that monthly average cost per use specifically refers to drug costs and excludes costs associated with physician visits for product administration. The sentence as presently written could be interpreted as representing total costs per month. Based on the Pharmacoepidemiology Report, injectable users were found to have a higher rate of health care utilization. Such non-drug related costs should then be included when comparing monthly cost for the products under review.

*RESPONSE: Sentence has been revised to: "The monthly average cost per user for the topical products (not including Androderm, Androgel pump or Axiron) is greater than either the injectable or oral products (\$115.80 vs. \$24.77 and \$65.16, respectively. Note that this represents drug costs only and excludes other healthcare related costs (e.g., physician visit for administration of injectable TRT)."*

- **Consolidated Report, Pg. 5: Reimbursement Options**
  - **Comment(s):** Three of the four reimbursement options recommended moving topical products to an Exception Access Program (EAP). Moving products to an EAP program however may create accessibility issues. For example, the Triptans drug class review completed by the ODPRN found that patients and doctors in particular find EAP to be cumbersome and a barrier. Doctors were also reported to be unaware that an EAP program exists. It should also be noted that the Qualitative Study Findings report indicates that there is uncertainty associated with the present Limited Use (LU) criteria and that criteria needed to be clarified to be applied correctly. In addition, in the Environmental Scan, it is reported that there is no consensus regarding the definition of a low serum testosterone level. Based on the Qualitative Study and Environmental scan, adding clarity to the present LU criteria appeared to be needed to ensure it is applied appropriately. Moreover, given that the ODPRN reports that there may be as many as 80% of men currently using TRT who do not meet the criteria, it is unclear how a move to EAP will increase adherence to the criteria.

*RESPONSE: A review of the criteria for either LU or EAP is currently being undertaken to help provide clarity for prescribers. Although the triptan report did highlight that some physicians are unaware of the EAP program for triptans, it is unknown whether this is an issue for other drugs or drug classes. As each EAP request is reviewed, adherence to criteria (e.g., level of testosterone, symptom presentation) is assured before approval of the TRT product is made. No changes have been made to the report.*

- **Consolidated Report, Pg. 13:** Current Utilization in Canada and Ontario

  - **Comment(s):** The ODPRN makes several provincial comparisons with respect to utilization and costs for TRTs across Canada. Given that criteria and listing types vary across public drug plans, the limitations of making such comparisons should be mentioned. The Consolidated Report gives the perception that all else is equal.

*RESPONSE: The pharmacoepidemiology TRT report has a methodological note before comparing provinces: "Public plan listings for Testosterone products vary across the provinces and formulation. Detailed information on public plan listings is provided in Appendix A". To address this limitation we have presented the numbers as rates among people eligible to receive the drug.*
  
- **Consolidated Report, Pg. 17:** There was substantial heterogeneity between trials due to variation in the inclusion criteria and outcomes of interest.

  - **Comment(s):** The specific outcomes of interest where substantial heterogeneity were observed should be specified. In addition, the limitations of performing network meta-analyses on the robustness of the analysis when substantial heterogeneity exists should be described.

*RESPONSE: The statement in question is from the consolidated report. We suggest the following modification to this statement: "There was clinical heterogeneity in the participants of the RCTs." For the each of the networks that included a closed loop, consistency was assessed and was satisfactory.*

*We have also performed a meta-analysis of TRT v. placebo to evaluate heterogeneity for serum testosterone level at three months. In particular, at the study level, for serum testosterone levels at three months, the results when Testim 1% gel was used with and without sildenafil were different. The forest plot for this analysis will be included in the final report.*
  
- **Consolidated Report, Pg. 21:** Pharmacoeconomics

  - **Comment(s):** In the base case analysis, it is assumed that extra testing would not occur with EAP. This was informed by the proportion of patients currently having a test while products were listed as LU benefits. The assumption is that patients without a test would not be eligible. This may overestimate savings associated with the EAP options. As part of the Sensitivity Analysis, this assumption was tested by increasing tests by 50%. It is recommended that the base case assumptions and those tested in sensitivity analyses be validated. Results of the sensitivity analyses should also be presented in the Executive Summary, in addition to major limitations associated with the analyses.

*RESPONSE: It is unclear what is meant by validation as this could only be conducted through a natural experiment of moving products to EAP and seeing what happened. A comment relating to the sensitivity analysis is already within the Executive summary.*



## Pharmacoeconomics Team

- The ODPRN states that given the fact that a “diagnosis of hypogonadism is not well captured in administrative databases, the sensitivity and specificity are unknown, and therefore, some misclassification of diagnoses is possible”. This, if not adjusted into the BIA, will significantly skew the overall results (costs and savings), conclusions and final recommendations to the Ontario MOH.

*RESPONSE: We adopted an approach whereby we assumed all patients who had a testosterone test prior to initiation of therapy would have tested positive and therefore had an appropriate diagnosis for treatment based on the current LU criteria. It is possible that some of those tested would not have tested positive. Thus, the budget impact (i.e. savings) may be even larger than forecasted. This was identified in the report and we tested the impact of this assumption assuming that 75% of tests are positive.*

- The ODPRN has used many different data sources to conduct the BIA (details of the data sources can be found on pages 7-8 in the Pharmacoepidemiology Unit). In the spirit of transparency and to validate the ODPRN’s BIA rationale, assumptions, results, sensitivity analyses and conclusions, it would be useful to understand which data sources were being used in which sections of the BIA, as this is not clear. Failure to provide additional details to address potential flaws in the BIA methodology could impact the Ontario Ministry of Health’s (MOH) understanding of the model as well.

*RESPONSE: On page 27 it is stated that: “The analysis used OPDP data on usage of testosterone replacement therapy (oral, patch, topical, injection) from 2000-2013.” This is the sole source for all current prescribing data and as the data used for forecasting future costs. Data relating to Alberta, Manitoba and Nova Scotia were as reported in the Pharmacoepidemiology report. Data for the use of testosterone tests were obtained from the Pharmacoepidemiology unit through analysis of OPDP data linked to administrative data relating to laboratory reimbursement. We have added sentences clarifying these data sources.*

- During the ODPRN stakeholders meeting, the ODPRN confirmed that the number of laboratory tests estimated was derived from the OHIP database. The ODPRN also agreed that OPDP patients may have had a private laboratory test done and therefore, the assumptions made in the BIA surrounding the type of test (i.e. TT, BioT) and the number of tests done is incomplete, meaning the total number of patients tested (i.e. < 1/3 of new users) is very likely understated.

*RESPONSE: We disagree that there would have been a high number of patients undergoing a private laboratory test. Analysis took the conservative approach (i.e. underestimating the number of ineligible patient’s and hence the budget saving from move to EAP) by assuming that*

*all patients who had undergone a lab test would be eligible. We have added a comment on this in the report.*

- Pg. 27: The BIA to forecast future OPDP expenditures used OPDP data of TRT usage, stratified by age covering the period of 2000-2013 and employed exponential and power models for beneficiaries aged < 65 years and > 65 years of age, respectively. A stakeholder recommends that the ODPRN review 2014 IMS/Brogan OPDP claims data since our review of this data clearly indicates a deceleration in TRT prescriptions and costs, which may be explained by the recent regulatory events surrounding this class of medication as a whole. With this in mind, the models used in the ODPRN's BIA, as well as the future expenditures calculated, should capture more recent claims data as we believe that the current BIA's forecasted expenditures and savings are overstated. A stakeholder acknowledges that IMS/Brogan OPDP claims data is only available for the first half of the year; however, projections can be made to estimate future growth and perhaps provide a more conservative and thus realistic prediction of future OPDP growth and expenditures.

*RESPONSE: Our analysis was conducted based on the available data at the time of the analysis. As such, updates to the analyses and dataset are not possible given the timelines to complete the project.*

- P. 28:
  - Assumption # 2: The ODPRN assumes that there will be no extra testing with the proposed EAP programs. A stakeholder disagrees with this statement since there may be current patients who were not tested initially but will be tested under the new EAP program. A stakeholder recommends that the potential costs for additional testing be included in the BIA.

*RESPONSE: Under the existing listing arrangement, to be eligible patients should have been tested. We therefore assumed all those that were tested prior to commencement of treatment were eligible under the proposed EAP criteria. We explored the sensitivity of this by assuming an increase in testing. A comment on the relatively low cost of testing compared to treatment has been added to the Consolidated Report.*

- Assumption # 4: The ODPRN assumes that the relative use between products not moved to EAP will remain as is. A stakeholder disagrees with this statement. It could be argued that physicians will be more inclined to change their prescribing behavior in favor of a TRT that does not create additional restrictions to access. A stakeholder recommends that the potential costs for switching from

“restricted” to “unrestricted” TRT be included in the BIA.

*RESPONSE: We did assume that physicians would be more likely to prescribe therapies that were not under EAP thus changing the relative use between therapies under EAP and those not under EAP. We also assumed that when multiple therapies were available under EAP the relative use of these would be the same when they were available under LU.*

- Sensitivity Analysis: A stakeholder would like more details surrounding points 1 and 2. What is the 75% and 50%, respectively, based on? Regarding point # 3, a stakeholder recommends that the cost of testing to confirm diagnosis be incorporated into the BIA.

*RESPONSE: It is unclear what more details are requested. We attempted to simulate what would happen if products were moved to EAP. To do so we needed an estimate of the % of users likely to meet EAP criteria – to do this we used data on laboratory test utilization prior to commencement of therapy and took the conservative approach (i.e. underestimating budget impact) of assuming all test were positive. We assumed there would be no extra testing with EAP as the LU criteria currently clearly require laboratory testing prior to commencement of therapy. We tested both these assumptions using alternative assumptions to assess the sensitivity to these assumptions.*

- Did the pharmacoeconomic analyses consider the health care utilization costs of physician visits for patients who are receiving injectable treatments?

*RESPONSE: Due to the lack of data, these costs were not incorporated.*

## Environmental Scan

- Pg. 28: The ODPRN concludes that there is little consistency regarding patient adherence to TRT treatment. As a base case, we recommend that discontinuation (incl. failures)/adherence rates be considered in the final policy recommendations and incorporated into the budget impact analysis (BIA) (at the very least in the sensitivity analysis) in order to present a more realistic forecast.

*RESPONSE: Adherence/discontinuation rates for testosterone products are difficult to interpret. For example, one study showed that almost 60% of patients received TRTs in a cyclic fashion (i.e., used for a few months, stopped treatment and then restarted with the same dose and medication). Therefore, no changes have been made to the report.*



## Pharmacoepidemiology Team

- Pg. 3, paragraphs 2 and 3: The ODPRN concludes that usage of the injectable formulation is highest in the younger patient population (less than 65 years of age) and that these users have fewer lab tests, fewer co-morbidities, stay on treatment for longer periods and are the highest users of healthcare utilization resources. Further analysis of this patient sub-group may be warranted in order to ensure appropriate use of TRT. A stakeholder recommends that the impact of an increase in healthcare utilization resources should be factored into the BIA to offset the lower acquisition drug costs of the injectable formulations and the higher drug acquisition costs of the topical formulations.  
*RESPONSE: Further analyses are being considered for publication of the work. No changes have been made to the report.*
- Pg. 17: Summary of findings for Exhibit 5 and 6. A stakeholder would like to highlight that despite more restrictive TRT listing criteria in other provinces (except Quebec), these provinces are experiencing the same relative growth of TRT, which speaks to the increase in overall awareness of late onset of hypogonadism and patient need for treatment.  
*RESPONSE: Thank you for the insight. We have mentioned the growth across Canada. However, we do not have enough information to conclude for what these products are being used for in provinces other than Ontario (appropriate vs. inappropriate use). No changes have been made to the report.*
- Pg. 35: Summary of findings for Exhibit 19: Men aged 65 years and older have a higher use of topical agents compared with other TRT formulations and are as compliant as users of injections and slightly less compliant than users of oral TRT. This could suggest that older men prefer topical treatments since they are less invasive than injectable formulations and more effective than oral therapies. A stakeholder believes that is important to implement policies that allow patients to choose which TRT formulation they want and will use.  
*RESPONSE: Thank you for your comment.*
- A stakeholder recommends that the ODPRN review 2014 IMS/Brogan OPDP claims data since our review of this data clearly indicates a deceleration in TRT prescriptions and costs, which may be explained by the recent regulatory events surrounding this class of medication as a whole.  
*RESPONSE: We observed the same decrease in the first quarter of 2014, which is presented in our report. Unfortunately, we do not have more current data. I have added a point to the summary box highlighting this decline.*

### Qualitative Research Team

- What type of methodology is used to recruit patients?  
*RESPONSE: Individuals were recruited through various channels which included cold calling, email and faxing, recruiting through primary care and specialist clinics, recruitment letters sent through e-mail distribution lists of professional organizations and advocacy groups and snow ball sampling (which includes asking participants to connect with individuals they know who may be able to offer valuable insight to the issue for the purpose of recruitment to the study). Patients are interviewed until saturation (recurrent themes) is achieved.*
- How many patients and prescribers were recruited through the snowball methodology?  
*RESPONSE: No patients were recruitment via this methodology. The qualitative team noted that men are generally unwilling to speak about this topic with friends and family members. Two prescribers were recruited via the snowball methodology.*
- Generally, were physicians aware of which treatment options were covered?  
*RESPONSE: Yes, physicians were aware of the treatment options that are covered. If a patient had coverage, physicians may discuss alternative treatments.*

### Systematic Review Team

- Did the systematic review only include studies with drugs that were available on the market? If not, why was Axiron (?) not included?  
*RESPONSE: All treatments approved by Health Canada were included in the analyses, regardless of if they are or are not available on the market. Studies involving Axiron were likely not included because they didn't meet the inclusion criteria.*
- General comment: A stakeholder would like to share with the ODPRN that a new meta-analysis was published in October, confirming no increase in cardiovascular risk associated with TRT (Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Exp Opin. 2014; 13(10):1327-51).  
  
*RESPONSE: The review by Corona and colleagues is mentioned in the consolidated report and will be discussed in the final full report. While Corona and colleagues found no increased risk of cardiovascular events with testosterone replacement therapy (TRT), there are some important*

*differences with our study that should be considered:*

- *Our review was limited to TRT products approved in Canada; Corona and colleagues included all TRTs*
  - *Corona and colleagues included any length of TRT, while we included only trials with treatment for three months or longer*
  - *Corona and colleagues included both hypogonadal and eugonadal men, while our population was restricted to hypogonadal men (total testosterone < 350 ng/dl or free testosterone < 225 pmol/l)*
- Pg. 7, 2<sup>nd</sup> paragraph, “Results”: “Seven studies (4, 5, 7, 9, 21, 25, 29) reported a measure of physical fitness as their primary outcome (e.g. muscle strength, as measured by leg press, lean body mass)”. Given the number of studies that evaluated this primary outcome, a stakeholder would like to know why this specific end-point was not selected as part of the ODPRN’s inclusion criteria.

*RESPONSE: The outcomes for evaluation in this review were selected a priori in discussion with clinical experts. Outcomes related to physical fitness were not identified as high priority in the scoping review. Our statement about physical fitness was intended to provide context about the studies that were identified during the review. In addition, the measures of physical fitness in the identified trials were varied and were reported as different outcomes in the included trials (e.g., leg press, lean body mass), not as a single outcome.*

- Pg. 11: “Quality of Life”: A stakeholder would like to highlight a discrepancy in the number of studies cited here. A total of 10 studies is mentioned, where 2 studies were excluded, which should total 8 studies and not 6 studies as written. In addition, there are a total of 7 studies with reported results in both Exhibits 4 and 5.

*RESPONSE: The total number of studies that reported quality of life was 10. Two were excluded, leaving eight studies for evaluation (Exhibit 5, Column 1). Seven treatments were evaluated in these eight studies (two studies compared Andriol, 160 mg/d with placebo). Exhibits 4 and 5 show the results for these seven treatments.*

- Pg. 28, “Key Messages”, 6<sup>th</sup> bullet point: The paragraph summarizes that 1) in head to head comparisons AndroGel 1% was associated with more favorable serum testosterone levels and Andriol was associated with less favorable serum testosterone levels at 3 months and 2) there were few significant differences among types of TRT for quality of life, erectile dysfunction, libido and depression. A stakeholder would like to point out that regardless of outcomes, Andriol failed to achieve its primary efficacy endpoint (i.e. normal serum testosterone levels), a current requirement for listing and reimbursement on the Ontario

Public Drug Program (OPDP). Thus, it could be argued that Andriol (and its generic equivalents, PMS-testosterone and Taro-testosterone) would not attain a positive listing recommendation from the OPDP or any other provincial drug plan if the file were reviewed today. A stakeholder feels strongly that this fact should be taken into consideration when the ODPRN makes its final recommendations to the OPDP's Committee to Evaluate Drugs (CED).

*RESPONSE: We have re-analyzed the data for serum testosterone levels after three months of treatment and have made a correction to the data. The revised version of Exhibit 4 is below.*

*We have also created a table to show the "after treatment" differences in each of the primary studies that went into this analysis. Only one study evaluated the effects of Andriol (120 mg/d) on serum testosterone levels at three months (Boyanov 2003). The authors reported a significant difference at the end of study between changes from baseline in the Andriol group and the control group ( $p < 0.05$ ).*

**Exhibit 4: Serum testosterone level, quality of life, erectile dysfunction, libido, and depression: mean (SD) differences from placebo based on network meta-analysis (updated)**

| Treatment                                | Mean difference (SD)           |                              |                                   |                     |                         |
|--|--------------------------------|------------------------------|-----------------------------------|---------------------|-------------------------|
|  | Serum testosterone level, 3 mo | Quality of life <sup>1</sup> | Erectile dysfunction <sup>2</sup> | Libido <sup>3</sup> | Depression <sup>4</sup> |
| Androderm, patch, 5 mg/d                 | 5.38 (2.54)*                   | ---                          | ---                               | -0.94 (4.26)        | -2.01 (4.75)            |
| Androgel 1%, gel, 50 mg/d                | 10.38 (2.72)*                  | 1.53 (19.54)                 | 3.29 (8.31)                       | -1.65 (4.30)        | 0.02 (3.41)             |
| Androgel 1%, gel, 100 mg/d               | 18.49 (3.42)*                  | ---                          | ---                               | ---                 | ---                     |
| Testim 1%, gel, 50–150 mg/d + sildenafil | 10.24 (2.84)*                  | 1.05 (18.87)                 | 1.40 (11.41)                      | 0.28 (5.24)         | ---                     |
| Testim 1%, gel, 50 mg/d                  | 2.28 (2.81)                    | ---                          | ---                               | -0.14 (5.03)        | ---                     |
| Androgel 1%, gel, 75 mg/d                | 7.53 (3.51)*                   | 2.49 (19.16)                 | ---                               | ---                 | -0.69 (3.43)            |
| Andriol, oral, 120 mg/d                  | 4.34 (2.68)                    | ---                          | ---                               | 0.97 (5.22)         | ---                     |
| Delatestryl, IM, 200 mg/2wk              | 15.67 (3.91)*                  | ---                          | ---                               | ---                 | ---                     |
| Testosterone enanthate, IM, 100 mg/wk    | 6.30 (3.19)                    | ---                          | ---                               | ---                 | ---                     |
| Testosterone enanthate, IM, 200 mg/2wk   | 8.65 (2.91)*                   | ---                          | ---                               | ---                 | -2.29 (3.36)            |
| Testosterone cypionate, IM, 200 mg/2wk   | -0.18 (3.27)                   | ---                          | ---                               | ---                 | ---                     |
| Andriol, oral, 160 mg/d                  | ---                            | -0.77 (13.51)                | -0.13 (11.48)                     | -1.11 (5.18)        | ---                     |
| Testim 1%, gel, 100 mg/d                 | ---                            | ---                          | ---                               | 0.51 (7.31)         | ---                     |
| Andriol, oral, 120–160 mg/d              | ---                            | -18.78 (18.97)               | ---                               | ---                 | ---                     |

|  |     |               |             |     |              |
|--|-----|---------------|-------------|-----|--------------|
| Testosterone undecanoate, oral, 160 mg/d | --- | -0.29 (19.35) | 3.62 (8.18) | --- | -3.10 (3.39) |
| Andriol, oral, 40 mg/d                   | --- | ---           | ---         | --- | -4.08 (3.40) |
| Testosterone enanthate, IM, 300 mg/3wk   | --- | ---           | ---         | --- | -1.20 (3.38) |
| Androgel 1%, gel, 5 mg/d                 | --- | -3.16 (18.78) | ---         | --- | ---          |

Note: IIEF = International Index of Erectile Function, IM = intramuscular injection, SD = standard deviation, SMD = standardized mean difference.

1. SMD translated to Aging Male Symptoms (AMS) Rating Scale.

2. SMD translated to IIEF erectile dysfunction domain.

3. SMD translated to IIEF sexual desire domain.

4. SMD translated to Beck Depression Inventory.

\*Statistically significant ( $p < 0.05$ ).

### Head-to-head comparisons of the testosterone treatments on serum testosterone level at 3 months (updated)

|    | 1     | 2     | 3   | 4   | 5     | 6     | 7     | 8   | 9     | 10    | 11    |
|----|-------|-------|-----|-----|-------|-------|-------|-----|-------|-------|-------|
| 1  |       |       | Red |     |       |       |       | Red |       |       |       |
| 2  |       |       | Red |     | Green |       |       |     |       |       | Green |
| 3  | Green | Green |     |     | Green | Green | Green |     | Green | Green |       |
| 4  |       |       |     |     |       |       |       |     |       |       | Green |
| 5  |       | Red   | Red |     |       |       |       | Red |       |       |       |
| 6  |       |       | Red |     |       |       |       |     |       |       |       |
| 7  |       |       | Red |     |       |       |       | Red |       |       |       |
| 8  | Green |       |     |     | Green |       | Green |     |       |       | Green |
| 9  |       |       | Red |     |       |       |       |     |       |       |       |
| 10 |       |       | Red |     |       |       |       |     |       |       |       |
| 11 |       | Red   | Red | Red |       |       |       | Red |       |       |       |

Treatments:

- |   |  |
|---|--|
| 1. Androderm, patch, 5 mg/d                 | 7. Andriol, oral, 120 mg/d                 |
| 2. Androgel 1%, gel, 50 mg/d                | 8. Delatestryl, IM, 200 mg/2wk             |
| 3. Androgel 1%, gel, 100 mg/d               | 9. Testosterone enanthate, IM, 100 mg/wk   |
| 4. Testim 1%, gel, 50-150 mg/d + sildenafil | 10. Testosterone enanthate, IM, 200 mg/2wk |
| 5. Testim 1%, gel, 50 mg                    | 11. Testosterone cypionate, IM, 200 mg/2wk |
| 6. Androgel 1%, gel, 75 mg/d                |  |

Summary of studies that reported serum total testosterone levels at three months

| Study           | Treatment 1                              | Treatment 2          | Comparison               | After treatment, mean (SD), nmol/L |             |             | Significant in original study                       |
|-----------------|--|----------------------|--------------------------|------------------------------------|-------------|-------------|---|
|                 |  |                      |                          | Treatment 1                        | Treatment 2 | Comparison  |   |
| Spitzer         | Testim 1% gel (50-150 mg/d) + sildenafil | NA                   | Placebo                  | 22.0 (7.7)                         | NA          | 11.8 (7.7)  | Yes   |
| Sheffield-Moore | TE, 100 mg/wk                            | NA                   | Placebo                  | 20.8 (2.9)                         | NA          | 12.1 (2.9)  | Yes   |
| Shores          | Androgel 1%, 75 mg/d                     | NA                   | Placebo                  | 15.6 (9.8)                         | NA          | 8.0 (2.8)   | Yes*  |
| Brockenbrough   | Testim 1%, 50 mg/d                       | NA                   | Placebo                  | 10.1 (2.2)                         | NA          | 7.8 (4.5)   | No  |
| Orengo          | Androgel 1%, 50 mg/d                     | NA                   | Placebo                  | 23.8 (4.9)                         | NA          | 12.8 (4.4)  | Yes   |
| Boyanov         | Andriol, 120 mg/d                        | NA                   | No treatment             | 15.4 (3.4)                         | NA          | 11.2 (3.16) | Yes   |
| Wang            | Androderm, 5 mg/d                        | Androgel 1%, 50 mg/d | Androgel 1%, 100 mg/d    | 14.5 (5.9)                         | 19.2 (9.1)  | 27.5 (9.9)  | T1 v. T2: Yes*‡<br>T2 v. C: Yes*‡<br>T1 v. C: Yes*‡ |
| Dobs            | Androderm, 5 mg/d                        | NA                   | Delatestryl, 200 mg/2 wk | 28.3 (5.8)                         | NA          | 17.9 (6.1)  | Yes*  |
| Clague          | TE, 200 mg/2wk                           | NA                   | Placebo                  | 19.5 (4.8)                         | NA          | 13.2 (2)    | Yes*  |
| Bhasin          | Androderm, 5 mg/d                        | NA                   | Placebo                  | 12.6 (5.4)                         | NA          | 7.6 (3.4)   | Yes*  |
| Sih             | TC, 200 mg/2wk                           | NA                   | Placebo                  | 9.7 (7.4)                          | NA          | 9.9 (3.7)   | No*   |

Note: TE = testosterone enanthate, TC = testosterone cypionate.

\*Calculated based on reported data.

‡Adjusted for multiple comparisons ( $p < 0.017$ )