Inspections, Compliance, Enforcement, and Criminal Investigations

Slate Pharmaceuticals 3/24/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Robert S. Whitehead, Chief Executive Officer
Slate Pharmaceuticals
318 Blackwell Street, Suite 240
Durham, NC 27701

RE: ANDA #80-911
Testopel® Pellets (testosterone), CIII
MACMIS #18378

WARNING LETTER

Dear Mr. Whitehead:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a sales aid (55789) (sales aid) for Testopel® Pellets (testosterone), CIII (Testopel), submitted by Slate Pharmaceuticals (Slate) under cover of Form FDA-2253. Additionally, through its routine monitoring and surveillance program, DDMAC has reviewed web pages[1] and a consumer video on the Testopel website (www.testopel.com)[2](video). The sales aid, web pages, and video are each misleading for one or more of the following reasons: they promote unapproved uses of Testopel, omit and minimize important risk information associated with Testopel, broaden the indication of Testopel, overstate the efficacy of Testopel, present unsubstantiated superiority claims for Testopel, omit material facts, present misleading convenience claims, present an unapproved dosing regimen for Testopel, and/or present other unsubstantiated claims about Testopel. Therefore, these promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a), (f)(1) & (n); and 321(n), and FDA implementing regulations. See 21 CFR 201.100(c)(1); 201.128; 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii), (xvii), (xviii); (e)(7)(i) & (viii).

We are extremely concerned by the breadth and scope of violations reflected in your promotional materials. The presentations seen throughout the cited pieces suggesting that Testopel is safer and more effective than has been demonstrated are very problematic from a
public health perspective given the limited indication of the drug and its risk profile.

Furthermore, you failed to submit the web pages and video to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i).

Reference is made to the teleconference between DDMAC and Slate on March 16, 2010, during which DDMAC outlined its serious concerns with the pieces referenced above. DDMAC acknowledges that, following the teleconference, Slate committed to comply with DDMAC's request to immediately cease the use of these materials and to initiate a review of other promotional materials for the same or similar violations. We appreciate this commitment and the steps that Slate has taken thus far to address some of the issues outlined ir this letter.

Background

According to its FDA-approved product labeling (PI), Testopel is approved for the following indication:

Males
Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone;

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

b. Hypogonadotrophic hypogonadism (congenital or acquired) – idiopathic gonadotropin or LHRH deficiency, or pituitary – hypothalamic injury from tumors, trauma, or radiation.

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

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

The use of Testopel is associated with a number of serious risks. Testopel is contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate, and in pregnant women (as it presents a potential hazard to the fetus). The PI also includes warnings regarding hypercalcemia in patients with breast cancer, development of peliosis hepatitis (which can be a life-threatening or fatal complication) and hepatic neoplasms (including hepatocellular carcinoma) with prolonged use of high doses, increased risk for the development of prostatic carcinoma, edema with or without congestive heart failure in patients with preexisting cardiac, renal or hepatic disease, development of gynecomastia, and acceleration of bone maturation without compensatory gain in linear growth in children and the potential for serious adverse health effects if Testopel is used for purposes not shown to be safe and effective (i.e., for the enhancement of athletic performance).

According to the PRECAUTIONS section of the PI, Testopel implantation has much less flexibility for dosage adjustment than oral administration of or intramuscular injections of oil solutions or aqueous suspensions, requires surgical removal if testosterone should be discontinued, and carries a risk of sloughing out of the skin. In addition, the PI includes precautions regarding frequent or excessive erections of the penis, nausea, vomiting changes in skin color, ankle swelling, and the need for bone development checks in adolescent patients. The PI also includes precautions regarding drug interactions with oral anticoagulants, oxyphenbutazone, and insulin. Moreover, the PRECAUTIONS section of the PI discusses the need for various laboratory tests, specifically: periodic liver function tests because of associated hepatotoxicity; x-ray examinations of bone age every six months during treatment of prepubertal males; and periodic hemoglobin and hematocrit levels to detect polycythemia in patients who are receiving high doses of androgens.

Furthermore, Testopel includes several adverse reactions including, but not limited to, excessive frequency and duration of penile erections, hirsutism, male pattern of baldness, acne, alterations in liver function tests, suppression of clotting factors II, V, VII, and X, polycythemia, increased or decreased libido, headache, anxiety, depression, generalized parethesia, inflammation and pain at the site of subcutaneous implantation, and anaphylactoid reactions.

According to the DOSAGE AND ADMINISTRATION section of the PI (in pertinent part):

The suggested dosage for androgens varies depending on the age, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions. The dosage guideline for the testosterone pellets for replacement therapy in androgen-deficient males is 150 mg to 450 mg subcutaneously every 3 to 6 months. Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower doses initially, gradually increasing the dose as puberty progresses, with or without a decrease in maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

Dosages in delayed puberty generally are in the lower range of that listed above, and for a limited duration, for example, 4 to 6 months.

. . .

Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months

Promotion of Unapproved Uses

As detailed below, the web pages and video misleadingly suggest several new "intended uses" for Testopel that the drug is not approved to treat.

Web Pages

Several web pages on the Testopel website present the following statements (italicized emphasis in original; bolded emphasis added):

• "Check back for a video of a **patient with depression** giving his personal perspective on how Testopel® helped him to reclaim his life. . . ." (see "Depression" web page)

• "Check back for a video of a **patient with erectile dysfunction** giving his personal perspective on how Testopel® helped him to reclaim his life. . . ." (see "Erectile Dysfunction" web page)

- "Check back for a video of **a patient with type 2 diabetes** giving his personal perspective on how Testopel® helped him to reclaim his life. . . ." (see "Type 2 Diabetes" web page)
- "Check back for a video of **a patient with HIV** giving his personal perspective on how Testopel® helped him to reclaim his life. . . ." (see "HIV" web page)
- "My doctor suggested testosterone **to help with my ED.** He explained my options and I choose Testopel® because it sounded the easiest. . . ." (see "Patient Stories" web page)

Additionally, the following claims are presented on the "TESTOPEL® FOR LOW T" web page (emphasis in original):

- "What are the benefits of Testopel® therapy?

. . . .

  - o Improved mood
  - o Increased sexual interest
  - o Restoration of erectile function
  - o Increased muscle mass
  - o Increased strength of bones."

The overall impression conveyed by the above claims misleadingly implies that Testopel can be used to treat the symptoms of depression, erectile dysfunction, type 2 diabetes, HIV, mood disorders, and loss in sexual interest, and that Testopel treatment results in an increase in muscle mass and bone strength. FDA is unaware of any data to support these claims and implications.

Video

The video presents the following statements made by Dr. Abraham Morgentaler, Associate Clinical Professor of Surgery (Urology) at Harvard Medical School, affiliated with Beth Israel Deaconess Medical Center and Founder and Director of Men's Health Boston, in which he promotes the use of Testopel (emphasis added):

- "I specialize in **sexual medicine** and in particular work around testosterone."
- "When we treat them [patients] and we get their levels back to normal -- the guys come back and they say 'I feel normal again.' Their strength may improve, their workouts at the gym may get better, **they start chasing their wives around the room a little bit** -- they just feel like guys again."

The totality of these claims misleadingly implies that Testopel can be used to treat sexual dysfunction. FDA is unaware of any data to support these claims.

The video also presents other statements by Dr. Morgentaler as well as a patient's testimonial about Testopel treatment. Dr. Morgentaler's statements include the following (emphasis added):

- "I had a patient just the other day who is a golf professional and he found **he just wasn't hitting the ball as far**. He had low testosterone."
- "Their **strength may improve, their workouts at the gym may get better** . . . ."

The patient's statements include the following (emphasis added):

- "I was **having trouble doing push ups,** I couldn't do more than five to six, and . . . I tried and it really bothered me."

The totality of these claims misleadingly implies that Testopel has a positive impact on the enhancement of athletic performance of professional (and non-professional) athletes, such that Testopel can improve physical strength in these patients. These claims are especially concerning because they contradict the Testopel PI; according to the WARNINGS section of the PI, "This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk for serious adverse health effects, **this drug should not be used for such purpose**" (emphasis added).

As detailed above, the webpages and video promote unapproved uses for Testopel; as a result, these promotional materials misbrand the drug because the approved PI for Testopel lacks adequate directions for the uses recommended in these promotional materials.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials.

Video

The video omits or minimizes serious risks associated with the use of Testopel. Specifically, the video fails to convey any risks specific to Testopel during the efficacy presentation of the video, which encompasses all but the last ten seconds of the video's two minute and nine seconds of running time. The only risk information presented is relegated to the end of the video, where it is unlikely to draw the viewer's attention. Furthermore, this information is presented in small print type in single-spaced paragraph format, with no accompanying audio presentation, and it appears on the screen for less than ten seconds, which does not allow adequate time for

viewers to read this information. As such, the presentation of this risk information lacks comparable prominence to the presentation of effectiveness information in the video.

Additionally, although the video presents some of the contraindications associated with Testopel, it completely omits the most serious and important warnings (i.e., hypercalcemia in patients with breast cancer; developmen of peliosis hepatitis and hepatic neoplasms with prolonged use; increased risk for the development of prostatic carcinoma; edema with or without congestive heart failure in patients with preexisting cardiac, renal, or hepatic disease; development of gynecomastia; and acceleration of bone maturation without compensatory gain in linea growth in children), precautions (i.e., less flexibility for dosage adjustment than oral administration of or intramuscular injections of oil solutions or aqueous suspensions; requires surgical removal if testosterone should be discontinued; carries a risk of sloughing out of skin; frequent or excessive erections of the penis; nausea; vomiting; changes in skin color; ankle swelling; the need for bone development checks in adolescent patients; drug interactions with various drugs; and the need for various laboratory tests), and adverse reactions (i.e., excessive frequency and duration of penile erections; hirsutism; male pattern of baldness; acne; alterations in liver function tests; suppression of certain clotting factors; polycythemia; increased or decreased libido; headache; anxiety; depression; generalized parethesia; inflammation and pain at the site of subcutaneous implantation; and anaphylactoid reactions) for this drug product.
In addition, some of Dr. Morgentaler's statements about Testopel during the efficacy presentation of the video further minimize the serious risks associated with Testopel. For example, Dr. Morgentaler states the following:

- "The convenience of the pellets can be that it's a treatment that may last for three to six months for some men. **So they [patients] can just come in, get treated, and go about their ways and not have to think about anything else."**

However, according to the PRECAUTIONS, Information for the Patient section of Testopel's PI, "The physician should instruct patients to report any of the following side effects of androgens: . . . Too frequent or persistent erections of the penis. Any nausea, vomiting, changes in skin color, or ankle swelling." In light of these risks post-Testopel implantation, it is misleading to imply that upon administration of the drug, patients can "go about their ways and not have to think about anything else." This statement is especially concerning coming from a healthcare practitioner, considering the potentially serious side effects patients may experience. The video also fails to inform patients that Testopel therapy may need to be discontinued, and the pellets removed, due to complications or side effects, according to the PRECAUTIONS section of the PI.

Sales Aid

Although the back cover of the sales aid presents some of the adverse events associated with Testopel, it completely omits the serious contraindications (i.e., in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in pregnant women), warnings, precautions, and additional adverse reactions for this drug product (see above). Because the sales aid omits these serious and important risks, it misleadingly suggests that Testopel is safer than has been demonstrated by substantial evidence or substantial clinical experience.

We note that the statement, **"PLEASE SEE ACCOMPANYING COMPLETE PRESCRIBING INFORMATION FOR TESTOPEL®"** (emphasis in original), is included in green print type at the bottom of the inside right-hand page of the sales aid. However, this is insufficient to mitigate the misleading omission of risk information from this promotional piece.

Web Pages

Several web pages on the Testopel website, including the "TESTOPEL® FOR LOW T" and "Patient Stories" web pages, fail to disclose any risk information for Testopel. We note that the website includes links to "Prescribing Information" and "Important Safety Information" at the very bottom of the web pages in small font, and the "TESTOPEL® FOR LOW T" and "Patient Stories" web pages also include a "Safety Information" link on the right-hand side of the page. However, these links do not mitigate the misleading omission of risk from these pages. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any effectiveness or safety claims made in that part (See 21 CFR 202.1(e)(3)(i)).

In addition, the "Important Safety Information" webpage further minimizes the risks associated with Testopel. This web page contains a minimal disclosure of information relating to the contraindications for Testopel but entirely omits the warnings, precautions, and adverse reactions (see above) associated with the use of Testopel

We are very concerned from a public health perspective about your omission and minimization of risk information throughout the Testopel website, as it serves to severely minimize the risks associated with the use of Testopel.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. As discussed above, the web pages and video include broad references to possible uses of Testopel (including unapproved uses). The sales aid includes claims that Testopel is "the only FDA approved implantable testosterone pellet" and that Testopel is an "androgen formulation." The video includes the statement, "Testopel® is indicated for the treatment of conditions associated with a deficiency or absence of endogenous testosterone," which is presented in small print type under the header "IMPORTANT SAFETY INFORMATION" during the last ten seconds of the

video. However, the web pages, video, and sales aid all fail to disclose the full indication for Testopel, including the important limitations to the indication. As a result, these promotional materials suggest, among other things that Testopel is approved to treat all conditions or patients for testosterone replacement. However, Testopel is only indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone with specific material limitations (see Background section above).

Regarding the video, we note that it includes the statement, "See Accompanying Full Prescribing Information" at the end of the "IMPORTANT SAFETY INFORMATION" section. In addition, we note the sales aid includes the statement, "**PLEASE SEE ACCOMPANYING COMPLETE PRESCRIBING INFORMATION FOR TESTOPEL®**" (emphasis in original) in green print type at the bottom of the inside right-hand page of the sales aid. However, these statements do not mitigate the misleading omission of Testopel's full indication from these pieces, includin important limitations.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Sales Aid

The sales aid for Testopel presents the headline claim, **"RECLAIM YOUR LIFE™**," (emphasis in original) in conjunction with three graphic images of a man jogging, a man playing with a child, and a man kissing a woman

Web Pages

The "Depression," "Erectile Dysfunction," "Type 2 Diabetes," and "HIV" web pages present the following statements (emphasis added):

• "Check back for a video of a patient with depression [erectile dysfunction, type 2 diabetes, or HIV] giving his personal perspective on **how Testopel® helped him to reclaim his life.**"

In addition, the "Patient Stories" web page includes the following testimonial (italicized emphasis in original; bolded emphasis added):

• "My son suffers from Klinefelter's syndrome. Like any 14 year old, he just want[s] to do the same things as his friends – to be "**normal."** Rubbing on his medication every day was always a problem and his levels were all over the place. **Testopel® has been a life saver** for him and our family. For mothers of Klinefelter's sons everywhere, thank you Slate!"

Video

Furthermore, the video presents statements by Dr. Morgentaler and a patient on Testopel treatment. Dr. Morgentaler's statements include the following (emphasis added):

• "When we treat them [patients] and get their levels back to normal -- the guys come back and say, '**I feel normal again**.'"

The patient's statements in the video include the following (emphasis added):

• "My symptoms were really slowing down -- I was feeling old."
• "Before this my brain was slowing down, and I didn't want to do things, you know. But **now I got a lot of get up and go, and I want to do** . . . **things all the time** . . . ."

The above claims in the sales aid, web pages, and video imply that an outcome of treatment with Testopel is the ability for patients to resume their "normal" activities and lifestyle (i.e., to reclaim their lives). FDA is not aware of any studies that measured these outcomes or any other evidence to support such effects of Testopel treatment. If you have such evidence, please submit it to FDA for our review. We further note that Testopel treatment is associated with serious warnings, such as prostatic hypertrophy and prostatic carcinoma and edema with or without congestive heart failure (see Background section above), any of which can negatively affect a patient's everyday activities or lifestyle.

Unsubstantiated Superiority Claims/Overstatement of Efficacy

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Sales Aid

The sales aid includes the following claims that compare the efficacy of Testopel to other testosterone treatment (emphasis in original):

- "**ONLY TESTOSTERONE PELLETS YIELD SERUM TESTOSTERONE LEVELS WITHIN NORMAL RANGE FOR SEVERAL MONTHS"[3] (inside page left-hand side)**
  - "By day 2 post pellet insertion all patients had reached a serum T level plateau."[3]
  - "Testosterone levels remained above the lower limit of normal (10 nmol/l) for ~6 months."[3]

- o "**Author's Conclusion:** 'T-pellets are the androgen formulation with the longest biological action and strongest pharmacodynamic efficacy in terms of gonadotrophin suppression. The pharmacokinetic feature are advantageous compared to other T preparations and the patient acceptance is high.'"

The above claims are presented in conjunction with a graph titled, "**Testosterone Pellets Deliver Months of Serum T Levels Within Normal Range"** (emphasis in original), which displays levels of testosterone (nmol/L) over time (days). These claims and presentation are misleading because they imply that Testopel is clinically superior to other testosterone formulations because it is the only formulation that delivers testosterone levels within normal range for approximately six months. The Jockenhövel, et al. reference cited[5] does not constitute substantial evidence or substantial clinical experience to support this presentation. Generally, superiority claims must be supported by adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. The Jockenhövel, et al. study, however, was a single-dose, open-label, non-randomized pharmacokinetic study. Additionally, the study did not examine Testopel, but instead used a testosterone implant that is not approved in the United States (200 mg subdermal testosterone implants that are manufactured by Organon in Oss, the Netherlands). As such, it does not constitute substantial evidence to support the presentation in the sales aid.

Patient Preference Claims

Sales Aid

The sales aid includes the following claims that compare patient preference for Testopel to all other testosterone products (emphasis in original):

- "92% of men choose to continue with Testopel® rather than switch back to their prior testosterone therapy (front cover)
- "**9 OF 10 MEN PREFER TESTOSTERONE PELLET THERAPY OVER THEIR PREVIOUS FORM OF TREATMENT**"4 (inside page right-hand side)
  - o "Multiple studies demonstrate that men are so highly satisfied with testosterone pellet treatment that they choose to continue receiving pellets rather than returning to their previous form of therapy"[4]

These claims are misleading because they imply that the vast majority of patients prefer Testopel to all other forms of testosterone therapy that are currently on the market, when this has not been supported by substantial evidence or substantial clinical experience. The Seftel, et al. article cited in the sales aid includes references to the Jockenhövel, et al., Handelsman, Mackey, et al.,[5] and Handelsman, Conway, et al.[6] articles—all of which do not constitute substantial evidence or substantial clinical experience to support these claims. Generally, as stated above, superiority claims must be supported by adequate and wel-lcontrolled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. These references do not describe adequate and well-controlled head-to-head studies that evaluated patient preference for patients on Testopel compared to their previous treatments. In fact, these studies did not examine Testopel, but instead used testosterone pellets and dosage strengths that are not approved in the United States (20 mg, 100 mg, and 200 mg testosterone implants that are manufactured by Organon in Oss, the Netherlands). Additionally, the studies were published in 1996, 1997, and 1990, respectively, and, therefore, did not evaluate patient preference of newer formulations of testosterone in the current marketplace.

Furthermore, patient preference is a broad concept that encompasses multiple aspects of patient experiences, such as convenience, ease of use, dosing, dosage form, all aspects of efficacy, and adverse events. The cited references were not designed to evaluate such
patient experiences.

Omission of Material Facts/Unsubstantiated Convenience Claims

Video

The video presents the following statements made by Dr. Morgentaler about the superior convenience of Testopel compared to other testosterone formulations:

- "One of the advantages of that treatment is the guy doesn't need to treat himself everyday with a gel or a patch, and he doesn't need to get frequent injections."
- "The convenience of the pellets can be that it's a treatment that may last for three to six months for some men. So they can just come in, get treated, and go about their ways and not have to think about anything else."

Web Pages

Similarly, the "Patient Stories" web page includes the following statements (italicized emphasis in original; bolded emphasis added):

- "Worrying about my testosterone gel getting onto my wife or young kids was a problem. My wife was frustrated during our hectic mornings when I couldn't help by holding the baby. Testopel® just simplifies things. She's happy, I'm happy, the kids are happy."
- ". . . I choose Testopel® because it sounded the easiest . . . Still I was nervous for my first procedure. It was so simple. He was done before I knew it."

The "TESTOPEL® FOR LOW T" web page includes the following claim (emphasis added):

- "Unlike other testosterone medications, Testopel® is administered once every 3-6 months in a fast and simple in-office procedure."

Sales Aid

The sales aid includes the following claim (emphasis added):

- "Testopel® is administered in an **easy office based procedure** that takes **10 minutes or less**." (front cover)

In addition, the sales aid includes the claim, "**TESTOPEL® ELIMINATES MANY OF THE HASSLES ASSOCIATED WITH GEL THERAPY**," in conjunction with a table that presents the following statements (emphasis in original):

- **"Daily Application of Therapy Required";**
- **"Monthly Trip to Pharmacy";**
- **"Potential for Transfer of Medication to Others";** and
- "**Wait 5-6 hours Post Daily Application to Shower, Swim, or Perspire**."

The responses to each of these statements are "**NO**" for Testopel and "**YES**" for gel therapy (emphasis in original).

The overall impression of the above claims and presentations in the video, web pages, and sales aid is that Testopel is more convenient than gel therapy, a patch, or injectable treatments because Testopel eliminates many of the hassles or inconveniences associated with these other treatments. While we acknowledge that Testopel is administered differently than other therapies, FDA is not aware of any evidence that Testopel is more convenient than testosterone gel, patch, or injectable treatments for this patient population. While the sales aid, video, and web pages selectively present attributes that are the most favorable for Testopel compared to other therapies, they omit material information about other attributes of Testopel therapy, including serious risks, that could impede its convenience and are highly relevant to any decision about whether to prescribe or use Testopel or other treatments. For example, according to its PI, Testopel implantation requires a surgical procedure and must be implanted every three to six months, possesses less flexibility for dosage adjustment than oral administration or intramuscular injection of oil solutions or aqueous suspensions (i.e., gel therapy), requires surgical removal if Testopel should be discontinued, carries a risk of sloughing out of the skin, and may cause inflammation and pain at the site of implantation.

Thus, we are not aware of evidence to support the implication that Testopel is more convenient than other treatment options. If you have evidence to support such a claim, please submit it to FDA for review.

Moreover, the above claims suggest that Testopel treatment is an easy office procedure that takes ten minutes or less. We are not aware of any evidence to support the assertion that the administration of Testopel is "easy," "fast," or "simple" from either the healthcare provider's or patient's perspective. In fact, these claims are particularly troubling considering the factors that must be taken into account for the implantation process for Testopel (e.g., making an incision, the use of local anesthesia, whether the pellets are to be implanted in separate tracks, and the distance from the insertion site to the final location of the pellets), and the adverse events that could occur at the implantation site, such as "[i]nflammation and pain at the site of the subcutaneous implantation of testosterone containing pellets," according to Testopel's PI.

Misleading Comparative Claims/Promotion of Unapproved Dosing Regimen

Sales Aid

The sales aid presents the following claims (emphasis in original):

- "**TESTOPEL® IS HALF THE PRICE OF GEL THERAPY**
    - o When 8 pellets are administered, **TESTOPEL®** is half the cost of conventional testosterone gel therapy.

The above claims are presented in conjunction with a bar graph showing the average wholesale price (AWP) for 4.5 months of therapy, comparing eight pellets of Testopel ($700) to Testim® ($1,401) and AndroGel® ($1,515). The prices represented in the bar graph misleadingly imply that all costs associated with Testopel and gel therapy have been considered. However, the presentation does not disclose all costs involved with Testopel compared to gel therapy (e.g., healthcare provider office visits, surgical procedures to implant Testopel, management of adverse events, dosage adjustments, and laboratory monitoring).Thus, the claim that Testopel is half the cost of gel therapy is misleading.

Furthermore, these claims and presentation imply an unapproved dosing regimen for Testopel—i.e., that eight pellets of Testopel is the usual dosage for the drug's indicated use. However, according to the DOSAGE AND ADMINISTRATION section of Testopel's PI, the dosage guideline for replacement therapy in androgen-deficient males is 150 mg to 450 mg (**two to six 75 mg pellets) every three to six months**. We are not aware of any data to support a usual dosage of eight pellets for Testopel's approved indication.

Unsubstantiated Claims

The "TESTOPEL® FOR LOW T" web page includes the following claims (emphasis added):

- “Other than the initial stick of a needle used to numb the insertion area, **Testopel® insertion is pain-free.**”
- “Once implanted, most men have no awareness that the pellets are there.”

The above claims misleadingly suggest that the insertion of Testopel is “pain-free” (other than the initial needle stick) and that once Testopel is implanted, most patients will not feel the pellets. FDA is unaware of any evidenc to support that the administration of Testopel is “pain-free” or that once administered, most men are not aware that the pellets are implanted. These claims are further concerning in light of the adverse reactions associated with Testopel discussed above, such as inflammation and pain at the site of implantation.

Failure to Submit Under Form FDA-2253

Web Pages and Video

FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a complete transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product’s current professional labeling. A copy of the web pages and the video were not submitted to FDA under cover of Form FDA-2253 as required by CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the sales aid, web pages, and video misbrand Testopel in violation of the Act, 21 U.S.C. 352(a), (f)(1) & (n); and 321(n), and FDA’s implementing regulations. See 21 CFR 201.100(c)(1); 201.128; 202.1(e)(3)(i); (e)(5); (e)(6)(i), (ii), (xvii), (xviii); (e)(7)(i) & (viii). Furthermore, you failed to submit the web pages and video to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Slate submit a written response to this letter on or before April 7, 2010, with a complete listing of the promotional materials (with the 2253 submission date) that you have discontinued for Testopel as a result of the March 16, 2010 teleconference and this letter. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS# 18378 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Testopel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-80911	ORIG-1	SLATE PHARMACEUTICALS INC	TESTOSTERONE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS W ABRAMS

[1]"Depression" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories/depression. Last accessed on February 25, 2010.
"Erectile Dysfunction" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories/
erectile-dysfunction. Last accessed on February 25, 2010.
"HIV" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories/hiv. Last accessed on February 25, 2010.
"Important Safety Information" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/safety-information.
Last accessed on February 25, 2010.
"Patient Stories" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories. Las accessed on February 25, 2010.
"TESTOPEL® FOR LOW T" web page. Available at http://www.testopel.com/patient/testopel-for-low-t. Last accessed on February 25, 2010.
"Type 2 Diabetes" web page. Available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories/type-2-diabetes. Last accessed on February 25, 2010.

[2] This video is available at http://www.testopel.com/patient/testopel-for-low-t/patient-stories (last accessed on February 25, 2010); we note that the same video is also available on YouTube™ at http://www.youtube.com/watch?v=6L4Cp34EelM. Last accessed on February 25, 2010.

[3] Jockenhövel F, Vogel E, Kreutzer, et al. Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. *Clin Endocrinol.* 1996;45(1):61-71.

[4] Seftel A. Testosterone replacement therapy for male hypogonadism: Part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. *Int J Impot Res*. 2007;19(1):2-24.

[5] Handelsman DJ, Mackey M-A, Howe C, et al. An analysis of testosterone implants for androgen replacement therapy. *Clin Endocrinol (Oxf).* 1997;47:311-316.

[6] Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. J *Clin Endocrinol Metab.* 1990;71:216-222.

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