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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

RE: O1P-0302
Comments in Response to a Suitability Petition

To Whom It May Concern:

On July 10, 2001, TestoCreme, LLC, submitted a suitability petition that requested permission to submit an ANDA for TestoCreme® 5% (testosterone) Gel based on a determination of bioequivalence to AndroGel® 1% (testosterone gel), the reference drug. This submission was filed by the Dockets Management Branch on July 13, 2001. Based on the information contained in the suitability petition, TestoCreme® will contain a higher strength of testosterone than AndroGel and inactive ingredients that are substantially different than those found in AndroGel. Additionally, a metered dose dispenser will be used instead of unit dose packets.

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For the reasons provided below, FDA should not approve this petition because investigations must be conducted to demonstrate that the novel formulation of TestoCreme® is safe and effective. Safety and effectiveness cannot be demonstrated by bioavailability and bioequivalence studies. Further, it is likely that the novel formulation of TestoCreme® will require substantially different labeling than that approved for AndroGel®.

Statement of Grounds

AndroGel® is a hydroalcoholic gel containing 1% testosterone. When AndroGel® is applied to the skin it dries quickly and the skin serves as a reservoir for sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone that is applied to the skin is absorbed. In contrast, TestoCreme® is claimed to be an organogel with five times the strength of AndroGel®. The higher strength will permit application of a smaller volume of gel and arguably may result in bioequivalent absorption of testosterone. It is claimed that because less gel is applied, each application will require less skin surface which “should decrease the risk of transference of drug to the patient’s partner.” As required by law, the petitioner proposes to use essentially the same labeling as that used for AndroGel. The only proposed differences are those that describe the novel formulation and metered drug dispenser. Absent controlled investigations beyond bioequivalency studies, there is no basis to assume the labeling for AndroGel would be applicable to TestoCreme®.

A. Formulation-Safety Issues.

TestoCreme® is claimed to be an organogel rather than a hydroalcoholic gel. TestoCreme® gel contains no less than 14 inactive ingredients that are not found in AndroGel. See *Exhibit A* for qualitative comparison of the two formulations. There is no

assurance that the combination of those ingredients is safe for the use intended. Indeed, the differences in inactive ingredients raise numerous safety issues.

1. In clinical trials, AndroGel was shown to have application site reactions in approximately 5% of study participants depending on dosage. Numerous ingredients contained in TestoCreme® suggest that a similar safety profile may not exist for TestoCreme. For example, propylene glycol is a skin sensitizer. Butylated hydroxytoluene, sorbic acid and hydrogen chloride are skin irritants. At a minimum, skin irritation studies must be conducted to answer these questions. See Exhibit B for the International Chemical Safety Cards for these products. Erythema and edema are common reactions to sorbic acid contained in pharmaceutical creams. See Dora Soschin & James J. Leyden, Sorbic acid-induced erythema and edema, 14 J. Am. Acad. Dermatology 234 (1986) (Exhibit C).
2. The labeling for AndroGel contains a Contraindication for patients with known hypersensitivity to any of its ingredients including testosterone USP that is chemically synthesized from soy. TestoCreme® has 14 ingredients not found in AndroGel including soy lecithin. The addition of soy lecithin raises a potential safety risk in that it may contribute to an allergic reaction.
3. The labeling for AndroGel contains a Contraindication for female contact with the application site. Petitioner claims a higher concentration will permit a smaller application site and therefore, less potential for transference. While this might be true, it raises the obvious question of whether the higher testosterone concentration will result in greater transference if a female does come in contact with the application site. Further, because AndroGel is hydroalcoholic it dries

rapidly and actively delivers testosterone into the skin. This helps to limit the potential for transference. The same might not be true for the novel formulation of TestoCreme® which may be absorbed differently and reside on the surface of the skin. Additionally, the TestoCreme formulation contains three penetration enhancers (ethoxy diglycol, isopropyl palmitate and propylene glycol) that are not found in AndroGel. These penetration enhancers may enhance transference. Only clinical trials that measure transference can answer whether AndroGel and TestoCreme should have the same labeling to address transference issues.

4. Under Precautions, AndroGel labeling states, “[p]atients should cover the application site(s) with clothing after the gel has dried (e.g., a shirt).” The purpose of this direction is to minimize the possibility for testosterone transfer. Will clothing be equally effective at preventing transference of a highly concentrated gel with different penetration enhancers. Will differences in the drying characteristics between an organogel and hydroalcoholic gel make it more likely that an organogel (TestoCreme) will be absorbed in clothing? Only controlled investigations such as those described in the “Clinical Studies” section of AndroGel labeling can address these questions.
5. Under “Precautions” physicians are advised to inform patients that “[f]or optimal absorption of testosterone, it appears reasonable to wait at least 5-6 hours after application prior to showering or swimming. Nevertheless, showering or swimming after just 1 hour should have minimal effect on the amount of AndroGel® absorbed if done very infrequently.” In the absence of investigations in addition to bioequivalency studies, it is unknown whether that cautionary statement is equally applicable to TestoCreme’s novel formulation.

The above questions and others that can be posed about the adverse events that might be seen with TestoCreme are not intended to suggest that TestoCreme is unsafe. They do suggest that investigations beyond limited confirmatory testing is required to show that TestoCreme does not raise safety issues different from AndroGel. Based solely on information presented in the suitability petition, there is substantial reason to believe that the novel formulation of TestoCreme will require labeling different than Androgel. Under these circumstances, it would be inappropriate and inconsistent with precedent for FDA to approve the suitability petition and permit filing of an ANDA.

B. Formulation-Efficacy

The basic premise behind conducting bioequivalency studies is that if two drugs are bioequivalent; they are equally effective. Bioequivalency studies are typically conducted under controlled circumstances in either a single dose or in some circumstances multiple dose studies. If the dosage form and strength are identical it is reasonable to extrapolate from the controlled studies to use by the general population under uncontrolled circumstances. For example, a 25 mg tablet will deliver 25 mg of drug. However, when the formulation and delivery is different between drugs, this basic premise may not be true because every day usage might affect the amount of drug delivered and, therefore, bioequivalency and efficacy. In this regard, the petitioner indicated that a metered dose dispenser would deliver 0.5 grams of gel to deliver 50 mg of testosterone. Once dispensed the gel will be applied by hand and the hands washed with soap and water. In contrast, for the same 50 mg dose, AndroGel is dispensed in a 5 gram packet. If one assumes, for example, that only 50 mg of gel is lost in dispensing and application, 10% of the TestoCreme dosage is lost as compared to only 1% of the AndroGel dosage. In other words, due to variations in drug application that may occur in every day use, TestoCreme may deliver less of the anticipated dose than AndroGel. Given that some benefits of

testosterone appear to be dose dependent, e.g., bone mineral density, this difference in drug delivery could, over time, have an impact on efficacy.

C. Bioequivalency

In theory, it is conceivable that substantially different formulations of an active drug may be bioequivalent, i.e., there is no significant difference in the rate and extent of absorption of the active drug. Typically, bioequivalence is determined in a limited number of healthy volunteers in either single or multiple dose studies. Such studies, however, are inappropriate to determine whether TestoCreme Gel is bioequivalent to AndroGel. There is marked variation in absorption of testosterone in hypogonadal men, which may also be affected by diurnal rhythms of endogenous testosterone.. For example, at day 30 in the pivotal clinical study for AndroGel, the average daily testosterone concentration was 792 (+/- 294) mg/dl. Further, there is evidence that both the rate and extent of absorption of testosterone varies substantially between day 1 and day 30. Ronald S. Swerdloff et al., Long-term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men, 85 J. Clinical Endocrinology & Metabolism. 4500, 4504 (2002) (*Exhibit D*).

Additionally, different formulations and strengths of transdermal testosterone have different effects over time on free testosterone, DHT, the DHT/testosterone ratio, estradiol, FSH and LH. See Exhibit D. All of these factors may effect the safety and efficacy of the testosterone formulation. Any study to determine the bioequivalency of TestoCreme to AndroGel, the reference drug, should be designed to account for the large variation in individual patient absorption, diurnal rhythm, and differences in absorption over time. Multiple dosing periods are needed to evaluate and establish the therapeutic equivalence of these products. Additionally, testing should be done to ensure formulation differences do not affect other hormone levels that are related to testosterone levels.

Conclusion

TestoCreme 5% (testosterone) Gel's novel formulation raises issues of safety, efficacy and bioequivalency that cannot be addressed by standard bioequivalency studies. The additional studies needed to establish that TestoCreme is safe and effective are not merely confirmatory but essential to product approval. It is likely that if such studies are done that TestoCreme will not have the same labeling as AndroGel. FDA should not approve TestoCreme, LLC's suitability petition.

Sincerely,

A handwritten signature in black ink, appearing to read "Anspach". The signature is written in a cursive style with a long horizontal line extending to the left.

Jean-Louis Anspach
President & CEO
UNIMED PHARMACEUTICALS, INC.