FDA Panel: Two Thumbs Down for New Oral Testosterone Drugs

HYATTSVILLE, Md. — An FDA advisory committee voted 13-6 today against recommending the approval of the oral testosterone undecanoate capsule Tlando (Lipocine) for the treatment of hypogonadism in adult males.

Just one day prior, the same Bone, Reproductive, and Urologic Drugs Advisory Committee split on whether to recommend another oral testosterone undecanoate capsule, Jatenzo (Clarus Therapeutics), for the same indication. That vote was 10-9 against approval.

Both companies were seeking an indication for the class of approved therapies for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism.

Hypogonadism in males is marked by a lack of testosterone production, which may lead to symptoms such as infertility, osteoporosis, erectile dysfunction, emotional changes, and more.

Currently, there is only one available form of oral treatment approved for testosterone therapy, methyltestosterone (Android, Testred). However, it is seldom prescribed because of hepatotoxicity risk. Most commonly prescribed forms of treatment currently include injectable and topical treatments. The undecanoate formulation makes testosterone more lipophilic, allowing absorption through the intestinal lymphatic system and thereby bypassing liver metabolism.

Jatenzo

This is the second advisory committee review of Clarus' Jatenzo following an initial negative vote in September 2014, which led to the FDA denying approval that November. The agency told Clarus it would have to conduct a new phase III trial to address prior concerns in order to include food effect data, a revised starting dose and titration regimen, and ambulatory blood pressure monitoring.

As committee member Douglas C. Bauer, MD, of the University of California San Francisco, explained, "I voted 'no' because … the indication is the same as the existing preparations and we know there is huge off-label use … I think that's unacceptable, and I don't think that the sponsor's proposals to try to change that, frankly, are likely to be very successful."

"I'm very sympathetic to the fact that there's a population here that really clearly needs an oral preparation, and most, I think, would certainly be agreeable to a revised indication that could specifically target that low-risk cardiovascular population," he added. "I also agree that a randomized trial should be done; I would argue that it ought to be done pre-approval, not post-approval. I think cardiovascular clinical endpoints really do sway a clinician's practice habits, and I would favor that."

But temporary voting member Glenn D. Braunstein, MD, of Cedars-Sinai Medical Center in Los Angeles, disagreed. "I voted 'yes' for a number of reasons. Number one, I think the sponsors asked for this to be used in patients with both primary hypogonadism and secondary hypogonadism with structural defects, which is what the FDA requires. They did not ask for approval of this for the use in individuals with age-related low testosterone, [where] we do know testosterone is widely prescribed off-label … nonetheless, I think handling that problem is a different issue," he said. Braunstein added

that concerns over “potential, inappropriate off-label use” was not a reason to keep a drug off the market.

“I do think that patients with Klinefelter syndrome and other forms of classical hypogonadism really deserve an oral preparation that is efficacious,” he explained. “I think the safety can be monitored, and I strongly recommend a [risk evaluation and mitigation strategy] type program to look at safety in prescribing habits of the drug. Certainly for primary hypogonadism, one can require not only low testosterone but elevations of LH and/or FSH prior to starting therapy – there’s ways of addressing this.”

The clinical development program for Jatenzo included 10 studies, involving a total of 569 adult hypogonadal men, who received the investigational drug. The comparator group consisted of 215 men who received transdermal testosterone (Axiron). The studies included six phase II studies, and three phase III dose-titration analyses, along with the 2-month safety extension study.

The new phase III inTUne Trial met its primary efficacy endpoint, showing 237 mg of Jatenzo twice daily with food was able to achieve testosterone levels to a eugonadal range in 87.3% of the participants, exceeding the FDA’s primary endpoint target of 75% with similar findings in all sensitivity analyses. At baseline, all participants had consistently low morning serum testosterone levels less than 300 ng/dL at baseline.

However, compared with Axiron, the Jatenzo treatment group saw a significantly elevated daytime (mean difference 5.2 mmHg, 95% CI 2.3 to 8.2, P=0.0008), as well as a slightly elevated heart rate. Around 5.9% of the overall group receiving Jatenzo treatment had to begin a new antihypertensive medication or had a dose increase of an existing medication versus only 2.2% of the Axiron group, with similar findings in a safety population analysis.

“I do think that a cardiovascular safety study should be carried out – I’d accept a comparator study, even though I want to see a long-term, placebo-controlled cardiovascular safety study in testosterone in general,” Braunstein added. “I’d be willing to just look at this versus a comparator that’s on the market to see if there’s an increased risk because of hypertension, and lowering of HDL, and increasing of LDL and triglycerides over and above what is seen in some of the others.”

Tlando

This is also the second review cycle for Lipocine’s Tlando, after Lipocine’s initial new drug application from 2015 was rejected. The FDA determined the phase III trial supporting that application utilized an impractical titration regimen and failed to meet all three secondary endpoints.

Lipocine conducted two new phase III trials, which were included in the new application. Each had a 24-day treatment arm without dose titration, assessing Tlando at 150 mg three times daily (n=100) and 225 mg twice daily (n=95) taken with food in adult hypogonadal males.

The drug met its primary efficacy endpoint at the 225 mg twice-daily regimen with around 80% of participants achieving 24-hour average serum testosterone concentrations within the normal range between 300-1,080 ng/dL, prompting the proposal of this dosage for marketing.

Treatment-emergent adverse events in this trial occurred in about 21.1% of the participants, with one individual withdrawing due to a serious adverse event.

Lipocine’s clinical program also included the previously conducted 52-week trial, comparing Tlando with topical Androgel 1.62%, which found a notable increase in heart rate in both arms. Additionally, around 45% of participants receiving Tlando treatment had a reduction in HDL cholesterol

levels, falling below normal range by the conclusion of the study. During the vote, a commonly cited reason for not recommending the drug for approval were cardiovascular safety concerns and a lack of a blood pressure monitoring study.

Voting in support of Tlando’s approval, temporary voting member Stuart Howards, MD, of the University of Virginia in Charlottesville stated, “If I were king, I would only allow this drug to be administered by certified subspecialists who took a required course.”

Although they are not required to, the FDA often follows the advisory committee’s recommendations.

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