Transcript Details
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The Evolution of Testosterone Replacement Therapy

Announcer:
This medical industry feature, exploring "The Evolution of Testosterone Replacement Therapy," is sponsored by Clarus Therapeutics, Inc., driven by a mission to help men overcome the symptoms of hypogonadism.
Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Although testosterone was first discovered in the 1930's, it wasn't until recently that a unique formulation for oral testosterone replacement therapy became available. JATENZO (testosterone undecanoate) capsules is the first and only FDA approved oral softgel testosterone replacement therapy, for the treatment of men with hypogonadism, due to certain medical conditions. Today, we'll be taking a look at this development within the field, and discuss the treatment options currently available.

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me today is Dr. Paresh Dandona, an endocrinologist and professor at the University of Buffalo, and we also have Dr. Stanton Honig, Director of Men's Health Urology at Yale University.

Dr. Paresh Dandona and Dr. Stanton Honig are paid consultants for Clarus Therapeutics, Incorporated.

Dr. Dandona and Dr. Honig, welcome to you both.

Dr. Dandona:
Thank you.

Dr. Honig:
Thank you.

Dr. Caudle:
Before we begin, let's review the indication and boxed warning for JATENZO, which we'll be discussing later on today.

INDICATION
JATENZO® (testosterone undecanoate) capsules, CIII, is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

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

Limitation of use
Safety and efficacy of JATENZO in males less than 18 years old have not been established.

IMPORTANT SAFETY INFORMATION

WARNING: INCREASES IN BLOOD PRESSURE

• JATENZO can cause blood pressure or (BP) increases that can increase the risk of major adverse cardiovascular events or (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death.
• Before initiating JATENZO, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.
• Periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension and re-evaluate whether the benefits of JATENZO outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment.
• Due to this risk, use JATENZO only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

CONTRAINDICATIONS
JATENZO is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, in women who are pregnant, in men with a known hypersensitivity to JATENZO or its ingredients, or in men with hypogonadal conditions that are not associated with structural or genetic etiologies as JATENZO has not been established for these conditions and there is a risk of increased blood pressure with JATENZO that can increase the risk of MACE.

Dr. Caudle:
Now that we have that understanding, Dr. Honig, can you start us off by reviewing who needs testosterone replacement therapy?

Dr. Honig:
Sure. So men who present with hypogonadism should be treated with testosterone replacement therapy. There are two sets of guidelines, one from the Endocrine Society and the other from the American Urological Association. They both look at the diagnosis of hypogonadism, determined by the identification of symptoms and/or signs consistent with this condition, in conjunction with the measurement of two morning serum testosterone levels that are below 300 nanograms per deciliter.

Dr. Caudle:
Turning to you now, Dr. Dandona, why is it so important for conditions like hypogonadism to be managed by a physician with prescription treatment?

Dr. Dandona:
Hypogonadism is a clinical syndrome that results from a failure of the testicles to produce physiological concentrations of testosterone. Men who believe they may have testosterone deficiency need to be assessed by their health care provider. If they are diagnosed as having hypogonadism, the proven method to restore testosterone levels to the normal range is by treatment with an FDA-approved testosterone replacement therapy. And we need to be aware that there are two types of hypogonadism, primary hypogonadism which is due to disease of the testicles themselves, and secondary hypogonadism which is due to the disease in the hypothalamus and the pituitary.

Dr. Caudle:
And looking at this from your perspective, Dr. Honig, what are your thoughts on this condition's management in clinical practice?

Dr. Honig:
In urology, we see a large number of patients who have the signs and symptoms of hypogonadism, in conjunction with a low testosterone, and these patients may be candidates for testosterone replacement therapy.

Dr. Caudle:
For those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss the evolution of testosterone replacement therapy is Dr. Paresh Dandona and Dr. Stanton Honig.

So, Dr. Dandona, given what I mentioned earlier, about the long history of testosterone replacement therapy, can you speak to the timeline of therapeutic updates in a little more detail?

Dr. Dandona:
Yes. So, organotherapy was practiced as early form of testosterone replacement therapy. By that, it's implied sort of homogenates of the testicular tissue.

Identification of testosterone ushered in the modern era of testosterone replacement research, and this happened in mid-1930's, and the early formulations of testosterone replacement therapy addressed the poor oral viability- availability of native testosterone, but faced pharmacokinetic challenges, and we struggled to achieve sustained physiological levels of serum testosterone.

The pharmacokinetics and bioavailability data improved starting in 1990's, and many new routes of administration were developed between 1990's and 2010's. These included testosterone patches, testosterone topical solutions and gels, testosterone injectables and testosterone implants. The first oral testosterone therapy was in the form of methyltestosterone, and was approved in the 1970's, but

became obsolete due to hepatic toxicity.

Dr. Caudle:
That's interesting. And, if we fast forward to today, Dr. Honig, what should our colleagues be aware of regarding the current testosterone replacement therapy landscape?

Dr. Honig:
Well, we have a lot of different options that are available at the present time. They include patches, topical solutions and gels, injectables that include intramuscular injections, subcutaneous injections, and implants. And these have been most prescribed.

JATENZO has recently become available and gives our patients an oral option.

Dr. Caudle:
And just as a quick follow up to that, Dr. Honig, what do you think this oral therapy means for your patients?

Dr. Honig:
JATENZO is the first and only FDA-approved softgel testosterone undecanoate for testosterone replacement therapy in adult males, for conditions associated with a deficiency or absence of endogenous testosterone due to certain medical conditions.

JATENZO comes in three strengths, with five options, to give physicians options to help find a dose that fits patients' needs, and can be titrated to individualize the dosage of JATENZO, based on the patient's serum testosterone concentration response to the drug.

Dr. Caudle:
And before we wrap up, Dr. Dandona, do you have any additional thoughts on JATENZO and its potential impact on patient care?

Dr. Dandona:
As Dr. Honig mentioned, JATENZO allows for flexible dosing options. Previous formulations that were oral did not provide that predictability, and now for the first time, we have a preparation that is able to do so. In addition, JATENZO, when absorbed, passes into the intestinal lymphatic system, bypassing the liver, and thereby preventing hepatotoxicity.

Concerns with other treatment deliveries, highlighting that JATENZO is designed for oral testosterone delivery to avoid certain administration challenges, such as no injection pain, no procedures, no mess, no drying time, no transference to females or kids, no skin irritation, no gum irritation or disorders, and no nasal irritation.

Dr. Caudle:
Dr. Honig, anything to add?

Dr. Honig:
Yes, I'd just like to reiterate, for our patients who have signs and symptoms of hypogonadism, in conjunction with a low testosterone, below 300 nanograms per deciliter, that we have an oral testosterone undecanoate available to patients at the present time. And lastly, I'd like to remind my colleagues that they can view the full prescribing information on JATENZO.com.

Dr. Caudle:
Those are both great comments for us to consider, as we come to the end of today's program, and I'd really like to thank my guests, Dr. Paresh Dandona and Dr. Stanton Honig, for helping us better understand testosterone replacement therapy, and JATENZO. Dr. Dandona and Dr. Honig, it was great speaking with you today.

Dr. Dandona:
Thank you.

Dr. Honig:
Thank you.

Announcer:
And now, here's some important safety information.

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Limitation of use
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WARNINGS AND PRECAUTIONS

• JATENZO can increase blood pressure, which can increase the risk of MACE, with greater risk in patients with established cardiovascular disease or risk factors for cardiovascular disease. Before initiating JATENZO, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled. Monitor blood pressure approximately 3 weeks after initiating, increasing the dose, and periodically while on JATENZO, and treat any new or exacerbations of hypertension. Re-evaluate benefits and risks of continued treatment with JATENZO in patients who develop cardiovascular risk factors or disease. JATENZO is contraindicated in men with hypogonadal conditions such as "age-related hypogonadism" because the efficacy of JATENZO has not been established for these conditions and the increases in BP can increase the risk of MACE.
• Polycythemia may require a lower dose or discontinuation of JATENZO. Check hematocrit prior to initiation and every 3 months while a patient is on JATENZO and if hematocrit becomes elevated, stop JATENZO until hematocrit decreases to an acceptable level. If hematocrit increases after JATENZO is restarted, stop permanently.
• Some studies, but not all, have reported an increased risk of major adverse cardiovascular events or (MACE) in association with use of testosterone replacement therapy in men. Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use JATENZO. JATENZO can increase blood pressure, which can increase the risk of MACE.
• Monitor patients with benign prostatic hyperplasia or (BPH) treated with androgens due to an increased risk for worsening signs and symptoms of BPH. Patients treated with androgens may be at increased risk for prostate cancer and should be evaluated prior to initiating and during treatment with androgens. Monitor prostate-specific antigen or (PSA) levels periodically.
• Postmarketing reports of venous thromboembolic events or (VTE), including deep vein thrombosis or (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone replacement products like JATENZO. Evaluate patients with signs or symptoms consistent with DVT or PE and, if a VTE is suspected, discontinue JATENZO and initiate appropriate workup and management.
• Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions. If abuse is suspected, check testosterone levels to ensure they are in the therapeutic range. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.
• JATENZO is not indicated for use in women.
• Large doses of androgens can suppress spermatogenesis by feedback inhibition of pituitary FSH. Inform patients of this risk before

prescribing JATENZO.

• Prolonged use of high doses of methyltestosterone has been associated with serious hepatic adverse events. JATENZO is not known to cause these adverse events; however, patients should be instructed to report any signs of hepatic dysfunction and JATENZO should be discontinued while the cause is evaluated.

• Androgens, including JATENZO, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

• Gynecomastia may develop and persist in patients being treated for hypogonadism.

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

• Changes in the serum lipid profile may require dose adjustment of lipid-lowering drugs or discontinuation of testosterone therapy. Monitor the lipid profile periodically, particularly after starting testosterone therapy.

• Use JATENZO with caution in cancer patients at risk of hypercalcemia. Monitor serum calcium concentration regularly during treatment with JATENZO in these patients.

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

• Depression and suicidal ideation have been reported in patients treated with JATENZO in clinical trials. Advise patients and caregivers to seek medical attention for manifestations of new-onset or worsening depression, suicidal ideation or behavior, anxiety, or other mood changes.

ADVERSE EVENTS

The most common adverse events of JATENZO (incidence ≥2%) are headache (5%), increased hematocrit (5%), hypertension (4%), decreased HDL (3%), and nausea (2%).

DRUG INTERACTIONS

• JATENZO can cause changes in insulin sensitivity or glycemic control. Androgens may decrease blood glucose and may require a decrease in the dose of antidiabetic medications.

• Anticoagulant activity may be affected by androgens. More frequent monitoring of international normalized ratio or (INR) and prothrombin time are recommended in patients taking warfarin, especially at initiation and termination of androgen therapy.

• Use of testosterone and corticosteroids concurrently may increase fluid retention and requires monitoring in patients with cardiac, renal, or hepatic disease.

• Some prescription and nonprescription analgesic cold medications contain drugs known to increase blood pressure and concomitant use of these medications with JATENZO may lead to additional increases in blood pressure.

USE IN SPECIFIC POPULATIONS

The safety and efficacy of JATENZO in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing JATENZO to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. There is insufficient long-term safety data in geriatric patients utilizing JATENZO to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Please visit jatenzo.com/hcp for full prescribing information, including BOXED WARNING on increases in blood pressure.

This program was brought to you by Clarus Therapeutics. If you missed any part of this discussion, visit ReachMD.com. This is ReachMD. Be part of the knowledge.