T in Cheek: Buccal Testosterone as a New Treatment for Androgen Deficiency in Men

a report by
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DOI: 10.17925/USE.2006.00.1.85

Male androgen deficiency has become a burgeoning area of public and commercial interest. Male androgen deficiency (commonly called male hypogonadism) is a common and important endocrinological syndrome defined by signs and symptoms of androgen deficiency plus low serum testosterone levels. Klinefelter syndrome, the most common congenital form of male hypogonadism, occurs in one in 500 men. In addition, the prevalence of men with low testosterone increases dramatically with age. For example, the Baltimore Longitudinal Study showed that the prevalence of low serum total testosterone levels rises from 12% of men under age 50 to 50% of men over age 80; the prevalence is even higher based on serum free testosterone levels. Based on these data, there appears to be an epidemic of male hypogonadism. However, a more accurate estimation of the prevalence of male hypogonadism is derived from the Male Massachusetts Aging Study that looked at least three symptoms suggestive of hypogonadism plus low serum testosterone levels in a cohort of over 1,000 men followed for an average of nearly nine years. In this study, 4.1% of men aged 40–49 years and 9.4% of men aged 60–70 years were hypogonadal. The Baltimore Longitudinal Study and Male Massachusetts studies highlight both the high prevalence of male hypogonadism and the importance of defining this syndrome based on symptoms, signs and labs that are consistent with androgen deficiency.

The recent recognition has led to many innovations in the diagnosis and treatment of male hypogonadism. In this article, I will briefly review the diagnosis and treatment of male hypogonadism. I will discuss the potential use of buccal testosterone, one of the most recent approved androgen formulations, as an example of the promise and pitfalls of new therapies for male hypogonadism that are under development.

Diagnosis of Male Hypogonadism

The diagnosis of male hypogonadism depends on symptoms and signs suggestive of androgen deficiency; the symptoms and signs vary based on whether hypogonadism occurs pre- or post-pubertally (see *Table 1*). The symptoms and most of the signs of male hypogonadism are very non-specific. When a man presents with symptoms or signs of hypogonadism, the clinician should determine the serum testosterone level with an accurate and reliable assay. The initial testosterone measurement ideally should be done on a blood sample drawn in the morning. It is crucial to confirm any borderline low testosterone level with a second measurement from a blood sample drawn early in the morning because up to 30% of men may have a normal testosterone level on repeat measurement.

There is some controversy about the best method for measuring circulating testosterone levels. However, an Endocrine Society expert panel recently recommended that total serum testosterone level should be the initial diagnostic test. Automated assays for total testosterone are widely available and are generally accurate and reliable for the diagnosis of male hypogonadism. Most circulating testosterone is avidly bound to sex hormone-binding globulin (~40%) or weakly bound to albumin (~58%); only about ~2% is unbound or free. Bioactive testosterone (the amount of testosterone in the serum that is available to produce end-organ and tissue effects) is thought to be the sum of the free testosterone and weakly bound testosterone. Generally, total testosterone and bioactive testosterone levels parallel, but, in many clinical settings, sex hormone binding globulin levels may be significantly altered (e.g. older men, obese men, men with diabetes mellitus or who are treated with anti-epileptics or corticosteroids).

Accurate assays for free and weakly bound testosterone levels are not available at many local laboratories. There are accurate assays that directly measure serum free and weakly bound testosterone levels by equilibrium dialysis and ammonium precipitation respectively. It is less expensive and more convenient to use a validated formula to calculate free and weakly bound testosterone levels (using total testosterone, sex hormone-binding globulin and albumin levels plus known affinity constants). These calculated measurements correspond well to values obtained by the accurate direct assays, and national commercial laboratories offer these calculated free and weakly bound testosterone measurements. It may be useful in some cases to measure free and weakly

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Table 1: Symptoms and Signs of Pre- and Post-puberty Onset of Hypogonadism

Pre-pubertal hypogonadism	***Post-pubertal hypogonadism***
Eunuchoidal stature	*Normal stature*
Small testes (usually < 6cm³)	*Testes volume normal to slightly low (> 10cm³); soft*
Small penis (< 5cm)	*Penis normal size*
Lack of normal scrotal rugae and pigmentation	*Normal scrotal rugae and pigmentation*
Small prostate	*Normal prostate*
Scant facial, axillary and pubic hair	*Thinning of facial, axillary and pubic hair* *Lack of male pattern baldness*
High-pitched voice	*Normal voice*
Gynecomastia	*Gynecomastia*
Infertility	*Infertility*
Lack of libido	*Loss of libido*
Low bone mineral density	*Low bone mineral density*
Low muscle mass, high % body fat	*Low muscle mass, high % body fat*
Mild anemia	*Mild anemia* *Hot flushes* *Decreased sense of well-being*

bound testosterone levels when total testosterone levels are equivocal or in patients with suspected abnormalities in sex hormone binding globulin or albumin levels. Assays that measure free testosterone by an automated analog method are widely available, inexpensive and notoriously inaccurate; these assays for free testosterone should not be used.

When serum testosterone levels are found to be low, reversible causes should be identified and corrected if possible. For example, suppressed testosterone levels commonly occur with acute or chronic illness, medications such as corticosteroids or opiates, and many recreational drugs. Testosterone levels should be re-measured at least one month after resolution or in the quiescent phase of systemic illnesses and at least one month after cessation of opiates, corticosteroids and other drugs that affect the gonadal axis.

When the diagnosis of male hypogonadism has been confirmed and reversible causes have been corrected, then the clinician should measure serum gonadotropin (FSH and LH) levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. Serum LH level is a better marker for low testosterone secretion, but LH levels fluctuate significantly throughout the day. Reproducibly elevated LH levels confirm primary hypogonadism even when serum testosterone levels are low-normal, and elevated FSH levels are useful to verify primary hypogonadism.

For patients with primary hypogonadism, further evaluation is unnecessary. Karotyping for Klinefelter's syndrome, the most common form of primary hypogonadism is occasionally helpful, but serum karyotyping is costly. Most patients with Klinefelter's syndrome can be easily recognized based on physical exam findings (very small, firm testes) plus elevated serum gonadotropin levels. Patients with secondary hypogonadism (low or inappropriately normal gonadotropins levels) need a directed evaluation to exclude common causes such as a large pituitary tumor, hyperprolactinemia, hemochromatosis, Cushing's syndrome, and sleep apnea.

The most difficult diagnostic dilemma is the evaluation of an older man with slightly low testosterone levels and normal or slightly elevated gonadotropins levels. This clinical scenario is very common and has been dubbed andropause. Andropause has excited much interest in the lay press as a potential reversible cause of frailty associated with aging. The limited data currently available do not support widespread use of androgen supplementation to older men with slightly low testosterone levels.

Effects of Androgen Replacement Therapy

When the diagnosis of hypogonadism has been established, the clinician and patient must then determine if the benefits of androgen therapy warrant the potential risks and cost. For patients with unequivocal hypogonadism and no contraindications to androgen replacement therapy (e.g. untreated prostate or breast cancer, severe bladder outlet obstruction, untreated sleep apnea, or polycythemia), the benefits outweigh the risks of androgen replacement therapy. In some men with some manifestations of hypogonadism and borderline low testosterone levels, a trial of androgen therapy may be reasonable. Before beginning a trial of androgen therapy in instances where the diagnosis is equivocal, it is particularly important that the clinician document that he discussed the controversy and risks and benefits of androgen supplementation therapy with the patient.

Androgens affect a broad range of tissues, organs and physiological functions including sexual function, brain, muscle, bone, prostate, and the cardiovascular system. I will review briefly some of the important effects of androgens. There are many excellent recent reviews for readers interested in further details.

Benefits of Androgen Replacement Therapy

Sexual Function

Studies using a wide variety of formulations have shown an improvement of sexual desire, sexual satifaction and sexual performance. It is generally thought that younger

men may have normal sexual function with subnormal testosterone levels, but older men may have a dose-dependent effect of testosterone on sexual function.

Lean Body Mass, Strength and Fat Mass

Most studies have shown moderate increases (1–5kg) of lean body mass when androgen replacement therapy, but a few trials have shown no effect. Several small studies have shown increased strength in at least one muscle group and two studies have shown improvement in functional tests of leg strength and balance[5,15,16]. A recent large cohort study reported that hypogonadal older men have decreased balance and increased risk of falls, but it remains unclear of androgen therapy would reduce this risk of falls.

Bone Density and Fractures

Most trials show that testosterone replacement therapy increases bone mineral density in men with low baseline testosterone levels. It is likely that the duration and degree of testosterone deficiency, the mode of testosterone delivery and the average testosterone levels achieved during therapy affect the degree of bone mineral density increase. For example, studies using sublingual testosterone in younger hypogonadal men or a transdermal testosterone patch system in older hypogonadal men did not significantly increase bone mineral density in hypogonadal men whereas a study of intramuscular testosterone therapy given to older hypogonadal men resulted in very significant increases in spine and hip bone mineral density. It is likely that the lower pre-treatment and higher average treatment levels achieved in the intramuscular testosterone study explain the increased bone mineral density compared to the sublingual and transdermal testosterone trials. Although epidemiological trials suggest that male hypogonadism is an important risk factor for osteoporotic fracture, there has not yet been an adequately powered, long-term clinical trial of the effects of androgen replacement on osteoporotic fracture in hypogonadal men.

Mood and Sense of Well-being

The majority of clinical trials have demonstrated an improvement of mood and sense of well-being in hypogonadal men treated with a variety of androgen replacement formulations. Mood, like sexual function, tends to improve early in the course of therapy and then plateau.

STRIANT®
(testosterone buccal system) ℞
mucoadhesive

DESCRIPTION
Striant® (testosterone buccal system) is designed to adhere to the gum or inner cheek. It provides a controlled and sustained release of testosterone through the buccal mucosa as the buccal system gradually hydrates. Insertion of Striant® twice a day, in the morning and in the evening, provides continuous systemic delivery of testosterone. Striant® is a white to off-white colored, monoconvex, tablet-like, mucoadhesive buccal system. Striant® adheres to the gum tissue above the incisors, with the flat surface facing the cheek mucosa.

INDICATIONS AND USAGE
Striant® is indicated for replacement therapy in 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, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.
Hypogonadotropic hypogonadism (congenital or acquired) – idiopathic gonadotropin or LHRH deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation. These patients have low serum testosterone levels but have gonadotropins in the normal or low range.

CONTRAINDICATIONS
Androgens are contraindicated in men with carcinoma of the breast or known carcinoma of the prostate.

Striant® is not indicated for use in women, and must not be used in women. Testosterone supplements may cause fetal harm.

Striant® should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy.

WARNINGS
1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) have been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone is not known to produce these adverse effects.
2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.
3. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).
4. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
6. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients especially those with risk factors such as obesity or chronic lung diseases.

PRECAUTIONS
Striant® is applied to the upper gum just above the incisor tooth on either side of the mouth. Long-term data on gum safety is available for 117 patients and 51 patients with at least 6 months and 1 year of exposure, respectively. While the available data supports the overall oral safety of Striant®, longer-term data is not currently available and studies continue. Until such longer-term data become available, it is recommended that patients regularly inspect their own gum region where Striant® is applied. Any abnormal finding should be brought promptly to the attention of the patient's physician. In such circumstances, dental consultation may be appropriate.

General
The physician should instruct patients to report any of the following:
- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color, or ankle swelling.
- Breathing disturbances, including those associated with sleep.

Information for Patients
Advise patients to carefully read the attached patient leaflet accompanying each carton of Striant® blister packaged tablets.

Advise patients to regularly inspect the gum region where they apply Striant® and to report any abnormality to their health care professional.

Laboratory Tests
1. Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy.
2. Liver function, prostate specific antigen (PSA), cholesterol and high-density lipoprotein should be checked periodically.
3. Serum total testosterone concentrations may be checked four to twelve weeks after initiating treatment with Striant®. To capture the maximum serum concentration, an early morning sample (just prior to applying the A.M. dose) is recommended. In the infrequent circumstance where the total testosterone concentration in this sample is excessive, therapy with Striant® should be discontinued and an alternative treatment considered.

Drug interactions
Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and therefore, insulin requirements.

Corticosteroids: Concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation and should be administered cautiously, particularly in patients with cardiac or hepatic disease.

Drug/Laboratory Test Interactions
Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, mutagenesis, impairment of fertility
Animal data: Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human data: There were rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.
Striant® has been evaluated in patients for 1 year without reports of cancer related to the product. However, safety in patients beyond 1 year has not been established.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men.

Pregnancy Category X (see CONTRAINDICATIONS) – Teratogenic Effects: Striant® is not indicated for women and must not be used in women.

Labor and Delivery: Striant® is not indicated for women and must not be used in women.
Nursing Mothers: Striant® is not indicated for women and must not be used in women.

Pediatric Use: Safety and effectiveness in pediatric male patients below the age of 18 have not yet been established.

Geriatric Use: Of the total number of subjects in clinical studies of Striant®, 51 patients (16.5 percent) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, in Study 1, in patients 65 years of age and older, the total testosterone Cavg(0-24) value was higher by 12.7% compared to patients less than 65 years of age. In addition, the total T to DHT area-under-the curve ratio was lower in the older population compared to the younger population by 15.6%. These differences may not be clinically significant.

ADVERSE REACTIONS
In all clinical studies combined, a total of 308 patients were treated with Striant® for up to 12 months

Twelve Week Trials
In the pivotal, Phase 3, open-label controlled study (Study 1), 98 patients received Striant® for up to 12 weeks. Adverse events judged possibly, probably, or definitely related to the use of Striant® and reported by ≥ 1% of patients in Study 1 are listed in Table 2.

Table 2. Incidences of Adverse Events Possibly, Probably or Definitely Related to Use of Striant® in Study 1

Adverse event	Striant® (n=98)
Gum or Mouth Irritation	9.2%
Taste Bitter	4.1%
Gum Pain	3.1%
Gum Tenderness	3.1%
Headache	3.1%
Gum Edema	2.0%
Taste Perversion	2.0%

Please see "Gum-related adverse events and gum examinations" subsection for further information. The majority of gum-related adverse events were transient. Gum irritation generally resolved in 1 to 8 days. Gum tenderness resolved in 1 to 14 days.

The following adverse events judged possibly, probably or definitely related to the use of Striant® occurred in 1 patient each in Study 1: abdominal cramp, acne, anxiety, asthma (acute), breast enlargement, breast pain, buccal mucosal roughening, difficulty in micturition, fatigue, gingivitis, gum blister, gustatory sense diminished, hematocrit increased, lipids serum increased, liver function tests abnormal, nose edema, stinging of lips, and toothache.

There was one additional 12-week study in 12 patients. In this study, additional adverse events judged at least possibly related to Striant® and reported by 1 patient each included emotional lability and hypertension.

Long-Term Extension Trials
In two long-term extension trials, a total of 117 and 51 patients received Striant® for at least 6 months and 1 year, respectively.

Of 117 patients treated for at least 6 months, adverse events judged possibly, probably, or definitely related to treatment and reported by 1 patient each included: anxiety, buccal inflammation, depression, dry mouth, gastrointestinal disorder, gum redness, hypertension, infection, medication error, nausea, pruritis, renal function abnormal, stomatitis, taste bitter, taste perversion, and toothache. Polycythemia and increased serum prostate specific antigen (PSA) were reported in three and two patients, respectively.

Adverse events reported in the 51 patients treated for at least one year were similar to those reported after 6 months of treatment and lower in incidence.

Gum-related adverse events and gum examinations
In the pivotal controlled study (Study 1), all reported gum-related adverse events were collected and gum examinations were conducted at Baseline and every month thereafter.

In Study 1, a total of 16 patients reported 19 gum-related adverse events. Of these, ten patients (10.2%) reported 12 events of mild intensity, four patients (4.1%) reported 5 events of moderate intensity, and two patients (2.0%) reported 2 events of severe intensity. Most of these events were judged probably or definitely related to treatment with Striant®. Four patients (4.1%) discontinued treatment with Striant® due to gum or mouth-related adverse events including two with severe gum irritation, one with mouth irritation, and one with "bad taste in mouth". The majority of gum-related adverse events were transient. Gum irritation generally resolved in 1 to 8 days. Gum tenderness resolved in 1 to 14 days.

In Study 1, monthly gum examinations were conducted to assess for gingivitis, gum edema, oral lesions, ulcerations or leukoplakia. No cases of ulceration or leukoplakia were observed. No new oral lesions were observed. Gingivitis was common at Baseline (32.6%), and was reduced at Week 4 (10.2%), Week 8 (10.2%) and Week 12 (11.2%). Similar findings were seen for gum edema.

In the two long-term extension trials, gum examinations were conducted every 3 months while on treatment. In one of these trials, no patient had a gum abnormality, and in the other trial, moderate gingivitis and mild gum edema were reported by 1 patient each.

DRUG ABUSE AND DEPENDENCE
Striant® contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

OVERDOSAGE
There is one report of acute overdosage with testosterone enanthate injection: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

Oral ingestion of Striant® is not expected to result in clinically significant serum testosterone concentrations due to extensive first-pass (hepatic) metabolism.

DOSAGE AND ADMINISTRATION
The recommended dosing schedule for Striant® is the application of one buccal system (30 mg) to the gum region twice daily; morning and evening (about 12 hours apart). Striant® should be placed in a comfortable position just above the incisor tooth (on either side of the mouth). With each application, Striant® should be rotated to alternate sides of the mouth.

Upon opening the packet, the rounded side surface of the buccal system should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. Striant® is designed to stay in position until removed. If the buccal system fails to properly adhere to the gum or should fall off during the 12-hour dosing interval, the old buccal system should be removed and a new one applied. If the buccal system falls out of position within 4 hours prior to the next dose, a new buccal system should be applied and it may remain in place until the time of next regularly scheduled dosing.

Patients should take care to avoid dislodging the buccal system. Patients should check to see if Striant® is in place following toothbrushing, use of mouthwash and consumption of food or alcoholic/non-alcoholic beverages. Striant® should not be chewed or swallowed. To remove Striant®, gently slide it downwards from the gum towards the tooth to avoid scratching the gum.

HOW SUPPLIED
Striant® (testosterone buccal system) is for buccal administration only. It contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

Storage and Disposal. Store at 20–25ºC (68-77ºF) [see USP Controlled Room temperature]. Protect from heat and moisture. Damaged blister packages should not be used. Discarded Striant® buccal systems should be disposed of in household trash in a manner that prevents accidental application or ingestion by children or pets.

Rx only

Manufactured by:
Mipharm S.p.A, Milan, Italy

Manufactured for:
Columbia Laboratories, Inc.,
Livingston, NJ 07039

US Patent Numbers: 4,615,697; 6,248,358; others pending

STNT-XBS-002

Risks of Androgen Replacement Therapy

Prostatic Disease

Most studies of androgen replacement therapy have shown that androgen replacement therapy increases prostatic size within the normal range for age. Androgen replacement therapy does not appear to alter micturition or increase the incidence of bladder outlet obstruction symptoms, but virtually all clinical trials exclude men with pre-treatment symptoms or the diagnosis of bladder outlet obstruction. The effects of testosterone androgen replacement therapy on the risks of prostate cancer are controversial. Testosterone therapy probably does not cause *de novo* prostate cancer, but it can promote the growth of pre-existing prostate cancer. In general, androgen replacement therapy to older men stimulates a small increase in serum prostate specific antigen (0.3-0.6 ng/mL) that stabilizes after three to six months of therapy. If the serum prostate specific antigen increases more than 1.4 ng/ml during a year of androgen therapy, then a urological evaluation is indicated.

Cardiovascular Disease

Although male gender is an established risk factor for coronary artery disease, androgens do not appear to increase the risk of ischemic heart disease. Epidemiological studies show that the risk of coronary artery disease tends to occur more frequently in men with lower serum testosterone levels, and hypogonadal men with established coronary artery disease who are treated with androgen replacement therapy have fewer signs of ischemia during exercise than placebo-treated hypogonadal men with established coronary artery disease. In addition, androgen replacement therapy tends to have favorable effects overall on risk factors for coronary artery disease. Although androgen replacement therapy causes small, but significant decreases in high-density lipoprotein cholesterol levels, it causes larger decreases in atherogenic low-density lipoprotein cholesterol levels and causes favorable changes in body composition.

Erythropoeisis

Testosterone therapy stimulates erythropoiesis and may cause erythrocytosis, particularly in older men. Men who are treated with androgen replacement therapy should be periodically monitored with complete blood counts.

Treatment Options

There are now a myriad of androgen replacement treatment options: oral, buccal, transcutaneous (patches and gels), and short and long-acting injectable formulations that are being used in the US and around the world. It is beyond the scope of this brief review to discuss each of the formulations in depth, but each formulation has its advantages and disadvantages. I shall compare the most recently approved new formulation, buccal testosterone, with other approved formulations and will use it as a model for the promise and pitfalls of potential formulations of androgen replacement therapy that are being developed.

Buccal Testosterone

Steroid hormones are readily absorbed across the buccal mucosa into the systemic circulation and bypass first-pass hepatic metabolism. A small pilot study of a proprietary buccal testosterone tablet showed that peak testosterone levels were achieved within 30 minutes of application but testosterone levels returned to baseline within four to six hours. A newer proprietary buccal testosterone formulation, Striant®, was developed that is rapidly absorbed and maintains serum testosterone levels within the normal range for 12 hours. Initial clinical trials have shown that Striant (30mg every 12 hours) maintains serum testosterone levels in the normal range for a 24-hour period for 85–93% of hypogonadal men. The pharmakinetic profile compares favorably with transcutaneous testosterone patch and gel systems that are administered once daily on the torso. In a three-month safety trial, about 10% of patients withdrew because of application problems or intolerance with a few of weeks of intiating Striant, therapy. About 16% of the men who completed the three-month trial had either gum irritation or inflammation, and 3% withdrew because of oral adverse events.

The primary advantage of Striant is its mode of administration: most patients prefer an oral route for medications. There are other formulations of oral androgen replacement therapy: alkylated androgens and oral testosterone undecanoate. However, alkylated androgens cause hepatotoxicity, and Striant appears to have a longer-half and offer more stable testosterone levels than oral testosterone undecanoate. Although there have been no head-to-head comparison trials of Striant vs oral testosterone undecanoate, testosterone levels may vary significantly with oral testosterone undecanoate administration, and some men may have to take oral testosterone undecanoate three times daily. Many patients may prefer Striant over intramuscular injections of testosterone enanthate or cypionate every seven to 14 days because the discomfort of injections and to avoid the supraphysiological peaks of testosterone that occur two to three days after injection of these testosterone esters. ■

This article containing references is continued with references and an additional figure in the Reference Section on the website supporting this briefing (www.touchendocrinedisease.com).