

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-543

MEDICAL REVIEW

NDA 21543

Date submitted: August 7, 2002

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Review completed: June 13, 2003

Medical Officer Review

Sponsor: Columbia Laboratories
220 S. Orange Ave.
Livingston, NJ 07039

Drug: Generic: Testosterone buccal system
Trade: Striant®

Route of administration: Buccal

Dosage form: Buccal system

Strength: 30 mg.

Proposed indication:

Related NDAs: — , 21-454, 20-791. —

/S/

Harry Handelsman, DO
Medical Officer

/S/

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Executive Summary:

I. Recommendation

In the opinion of this reviewer, from a clinical perspective, the safety and efficacy of Striant® has been established, and this product should be approved for the indication "testosterone replacement therapy in men with a deficiency or absence of endogenous testosterone". A phase-4 commitment to collect long-term safety data in 50 patients in the ongoing safety trials has been obtained from sponsor. Negotiations have been successful in producing an acceptable label. For the clinical parameters, this label is essentially the same as that of currently marketed testosterone transdermal products.

II. Summary of Clinical Findings

A. Brief overview of the clinical program.

A new formulation of testosterone, as a buccal mucoadhesive system in the shape of a tablet, is proposed in this NDA to provide a controlled and sustained release of testosterone for absorption across the oral mucosa, thereby circumventing first pass (hepatic metabolism) and avoiding substantial degradation and elimination. Each system, containing 30 mg of testosterone, applied to gum tissue above the incisors twice a day (morning and evening), provides physiologic serum levels of testosterone.

In support of NDA 21-543, the sponsor submitted 5 clinical pharmacological studies (in both healthy females and hypogonadal men), and 4 completed clinical efficacy and safety studies in T deficient males (COL-1621-03, 04, -05, -07). In addition, safety update data from 3 ongoing clinical trials have been submitted (COL-1621-08, -09, -10).

Reviewer's Comment: This reviewer believes that data provided from adequate numbers of patients with adequate extent of exposure is regarded as being sufficient for this NDA.

B. Efficacy

The primary efficacy endpoint in these trials was the attainment and maintenance of serum T levels within the physiological range (3.0-10.5 ng/mL) following twice-daily application of this buccal product in T deficient males:

COL-1621-05: This was the pivotal Phase-3 trial of Striant® in 98 patients for 13 weeks. There were 72% primary efficacy responders (95% CI: 61-81%). In responders at Week 12, $C_{max(0-24)}$ was 9.96 ng/mL, $C_{min(0-24)}$ was 3.15 ng/mL, and $T_{max(0-24)}$ was 11.8 hours. The mean percentage of time, over the 24 hour sampling period, that T levels were in the normal range was 89%.

COL-1621-07: This was a smaller Phase 3 trial of Striant® in 33 patients for 7 days. Steady-state was achieved within 3 days, and the mean total T at all time points was within the normal range. $C_{avg(0-12)}$ was 5.98 ng/mL, and $C_{avg(12-24)}$ was 4.99 ng/mL.

COL-1621-03: This was a Phase-1 trial of Striant® in 12 patients for 12 weeks. Steady-state was achieved within the first 24 hours, and mean serum T remained between 4.43 and 7.21 ng/mL.

COL-1621-04: This was a Phase-2 trial of Striant® in 12 patients for 12 weeks. Total T was in the normal range at most time points and in all patients at follow-up. The mean total T at each time point ranged from 4.5-74 ng/mL, and the mean average total T over all visits was 5.6 ng/mL.

Reviewer's Comment: The results of these trials lead to the conclusion that this buccal product is effective in attaining and maintaining satisfactory serum T levels in hypogonadal men, and exhibits pharmacokinetics and pharmacodynamics similar to those seen with other approved transdermal testosterone systems.

C. Safety.

Data regarding clinical adverse events were derived from 7 clinical trials involving 323 patients with drug exposures from 7 days through 12 months. Safety variables assessed included clinical AE's, gum checks, hematology/clinical chemistry, serum hormones, vital signs, and ECG's. There was one reported death (auto accident). The most common AE's were application site reaction (11.8%), upper respiratory tract infection (6.3%), headache (5.6%), and dysgeusia (4.8%).

Reviewer's Comment: Relatively few of the reported clinical AE's were noted as severe in intensity, and neither the intensity nor the frequency of the AE's appeared to increase with duration of treatment. Patients with the shortest exposure had a reported AE incidence of 42.2 %, and patients with the longest exposure had an incidence of 28.5%. The application site reactions were generally tolerable. In this reviewer's opinion, the safety profile of Striant® is not of concern.

D. Dosing, Regimen, and Administration Issues.

The proposed dose of 30 mg of testosterone was derived from five Phase 1 and Phase 2 studies which demonstrated this dose to have the best balance between safety and efficacy in achieving stable physiological T levels.

E. Use in Special Populations.

Gender: Striant® is proposed for use in hypogonadal men. It should not be used in women.

Pediatric: The sponsor has requested to defer a pediatric study until such time as they receive approval for the adult indication. The Division agreed with that request.

Elderly: There is no data to suggest concern using this product in the elderly.

Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of this product has not been studied. However, in the pivotal Phase 3 trial, African-American men were adequately represented.

Renal/Hepatic Insufficiency: No pharmacokinetic studies were conducted in patients with renal or hepatic compromise.

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Clinical Review

1. Introduction and Background.

Various dosage forms of testosterone have been approved for the treatment of testosterone deficiency including injectable, oral, extended-release transdermal, pellet implantation, and topical gel. A new formulation, as a testosterone tablet in a buccal mucoadhesive system, is being proposed in this NDA to provide a controlled and sustained release of testosterone for absorption across the oral mucosa thereby circumventing first pass (hepatic) metabolism and avoiding substantial metabolism and elimination. As a consequence, this product is able to produce circulating testosterone concentration in hypogonadal males in the range of the physiological levels seen in healthy young males (3.0-10.5 ng/ml).

1.1. Proposed trade name of drug, class, proposed indication, dose and regimen.

Striant®, a preparation containing 30 mg of testosterone in a controlled and sustained release buccal mucoadhesive system, to be applied chronically, twice daily to gum tissue above the incisors, for the purpose of maintaining physiologic levels of testosterone in hypogonadal males.

1.2. State of armamentarium for indication.

The administration of exogenous testosterone, by various routes including oral, injectable, transdermal, and pellet implants, has been widely used as replacement therapy to treat hypogonadal males. These different routes have had varying degrees of clinical success and are associated with varied adverse events.

1.3. Milestones in product development.

A pre-IND meeting for this product was held on April 4, 2000, and IND# 60,906 was originally filed on August 31, 2000. A pre-NDA meeting was held on December 5, 2001, and NDA 21-543 was originally filed on August 8, 2002.

1.4. Foreign marketing history.

Striant® has neither been marketed nor is it pending approval outside the United States.

1.5. Important issues with pharmacologically related agents.

Prolonged use of orally active androgens have been associated with serious hepatic adverse events including cholestatic hepatitis and hepatic neoplasms. Elderly males treated with androgens may be at risk for stimulating indolent prostate cancer, and promoting or exacerbating symptoms of prostatic hyperplasia. Sleep apnea is potentiated in susceptible patients. Gynecomastia may occur.

2. Significant findings from Chemistry, Pharmacology, Toxicology, and Statistics.

There are no unresolved pharmacology, toxicology, or statistical issues. We await the recommendation of Compliance in regard to the drug manufacturing site in Milan Italy. Such is obviously required for drug marketing approval.

3. Human Pharmacokinetics

3.1. Pharmacokinetic Studies.

Three early Phase-1 studies were performed in females to minimize interference from endogenous testosterone (T):

Study COL-1621-01 (IS) evaluated serum T and DHT concentrations in 22 healthy females (ages 18-32) during and after a 12 hour application of the "initial" buccal bioadhesive product. Healthy women provided a Phase 1 physiologic model from which drug exposure could be easily gauged. All subsequent studies used the final "to-be-marketed" formulation. Comparisons between these formulations are seen in the following table:

Table 1.

Ingredients	Initial Formulation (mg)	To-Be-Marketed Formulation (mg)
Testosterone	30.0	30.0
Hydroxypropylmethylcellulose	—	—
Starch	—	—
Monohydrate Lactose	—	—
Anhydrous Lactose	—	—
Silicon Dioxide	—	—
Polycarbophil	—	—
Carbomer 934P	—	—
Talc	—	—
Magnesium Stearate	—	—
Total	—	—

A subset of 6 subjects participated in a PK study. The buccal systems were applied and removed 12 hours later. Blood sampling was performed at 0, 1, 2, 9, 10, 11, 12, 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 22, and 24 hours. The mean serum T was 7.68 ng/ml at 12 hours. Serum T fell to 0.25 ng/ml at 24 hours, and the elimination half-life of T ranged from 2.24-5.69 hours with a mean half-life of 3.3 hours.

Study COL-1621-01 (GB) evaluated serum T and DTH in 10 healthy women (ages 18-35) using a single dose applied for 12 hours, with sampling through 36 hours. PK parameters for total T are seen in Table 2.

Table 2.

Parameter	Mean	SD	Median	Minimum	Maximum
T _{max} (h)	11.1	1.75	12.0		
C _{max} (ng/ml)	7.34	3.0	6.85		
AUC ₀₋₂₄ (ng/ml)	64.74	32.60	52.72		
AUC ₀₋₁₂ (ng/ml)	52.35	25.52	45.60		
C _{avg} (0-12) (ng/ml)	4.36	2.03	3.80		
T _{1/2,z} (h)	2.87	1.58	2.56		

Study COL-1621-06 (CH) evaluated serum T in 8 healthy women (ages 21-29) using a single dose applied for 24 hours. A total of 21 samples were drawn at pre-defined times from 15 minutes prior to drug application to 36 hours post-application. Pharmacokinetic parameters for total T derived from this study are seen in Table 3.

Table 3.

Parameter	Mean	SD	Median	Minimum	Maximum
T _{max} (h)	10.	2.3	10.7		
C _{max} (ng/ml)	11.0	4.6	11.2		
AUC ₀₋₂₄ (ng/ml)	127.9	31.9	131.3		
AUC ₀₋₁₂ (ng/ml)	81.2	32.3	65.8		
C _{avg} (0-12) (ng/ml)	7.0	2.7	5.8		
C _{avg} (0-24) (ng/ml)	5.4	1.3	5.6		

Two additional Phase-1 PK studies were completed in T deficient men:

Study COL-1621-02 (GB) evaluated serum T and DHT pre-dose and following a 12 hour application of drug, and monitoring for an additional 12 hours in 12 hypogonadal men (ages 39-65). Summary parameters for baseline-corrected total T are seen in Table 4.

Table 4.

Parameter	Mean	SD	Median	Minimum	Maximum
T _{max} (h)	10.14	3.02	11.37		
C _{max} (ng/ml)	6.52	1.75	5.85		
AUC ₀₋₁₂ (ng/ml)	37.50	10.73	36.08		
AUC _{0-last} (ng/ml)	54.35	18.83	52.05		
C _{avg} (0-12) (ng/ml)	3.12	0.89	3.01		
C _{avg} (0-last) (ng/ml)	2.47	0.70	2.34		
T _{1/2,z} (h)	2.82	1.30	2.23		

Study COL-1621-03 (GB) evaluated the PK profile of T in 12 hypogonadal men (ages 26-61) following twice-daily application of drug for 7 consecutive days. Patients were monitored for 8 days at 34 pre-defined time-points. PK parameters for total T during and following 7-day repeated dosing are seen in Table 5.

Table 5.

Parameter	Mean	SD	Median	Minimum	Maximum
T _{min} (h)	12.94	5.02	12.76		
T _{max 1-7D} (h)	97.16	55.37	127.46		
T _{max 24} (h)	4.82	5.79	1.74		
C _{max 1-7D} (ng/ml)	9.13	2.08	9.10		
C _{min 24} (ng/ml)	7.74	1.74	6.95		
CL/F (ml/min)	8473	2276	8829		
AUC _{tot} (ng/ml)	1003.17	169.7	1006.30		
AUC ₁₂ (ng/ml)	68.18	17.59	64.52		
AUC ₂₄ (ng/ml)	126.42	35.28	113.27		
C _{avg 12} (ng/ml)	5.68	1.47	5.38		
C _{avg 24} (ng/ml)	5.27	1.47	4.72		
C _{avg tot} (ng/ml)	5.59	0.94	5.67		
T _{1/2, z} (h)	5.73	2.52	5.11		

Reviewer's Comments: These five Phase 1 PK studies demonstrated that total T and mean PK parameters were very similar in the single dose studies in healthy females and hypogonadal men. Using a normal laboratory reference range of serum T in healthy males of 3.0-10.5 ng/ml it can be seen that a single dose of drug maintained normal T levels for up to 16 hours, and steady-state levels were attained and maintained within 24 hours of twice-daily dosing. Serum T levels consistently returned to baseline within 12-24 hours of stopping treatment.

4. Description of Clinical Data and Sources.

The following materials were reviewed: 1) Summary of PK studies, and individual study reports of the 5 Phase 1 clinical pharmacology studies from the NDA. 2) Description and analysis of the available data from the 4 completed and 3 ongoing clinical efficacy and safety studies in T deficient males, from the NDA. 3) Adverse event data from the NDA.

5. Clinical Review Methods.

The pilot and additional PK studies were reviewed in detail and reviews of these can be found above in section 3, Human Pharmacokinetics. The clinical efficacy and safety trials and data reviews were reviewed in detail and these can be found in the Appendix. DSI audits were not required. Adequate documentation was submitted to comply with financial disclosure. Dental consult was obtained and reviewed.

6. Integrated Review of Efficacy.

6.1. Introduction.

The sponsor has demonstrated, in adequate open-label, multicenter clinical trials, that steady-state serum levels of T are achieved in hypogonadal men treated with twice-daily buccal applications of Striant®.

6.2. General Approach.

Efficacy was evaluated by assessments of serum T and its metabolite, DHT, as well as by their calculated PK parameters. The efficacy database consisted of 2 completed Phase 3 studies and 2 completed supporting clinical studies at centers in the US, UK, and Germany. Studies began in October, 2000 and ended in November, 2001, involving 155 enrolled and 139 evaluable patients.

6.3. Review of the Clinical Trials.

COL-1621-05 was a pivotal Phase 3, open-label, single-arm, multi-center evaluation of the efficacy and tolerability of Striant® following repeated twice daily dosing for 12 consecutive weeks in 98 hypogonadal men. Key inclusion criteria were: ages 18-80, serum T < 2.5 ng/ml, Body Mass Index (BMI) ≤ 35 kg/m², and adequate washout of any previous T replacement therapy. The primary efficacy endpoint was the percentage of responders having time-averaged-steady-state total T levels ($C_{avg\ 0-12}$ and $C_{avg\ 12-24}$) over the last 2 consecutive 12-hour dosing intervals within the physiological range and trough levels ≥ 3.0 ng/ml at Week 12. Supplemental primary efficacy endpoint responders were defined as those having the last 2 consecutive 12-hour dosing intervals ($C_{avg\ 0-24}$) within the physiological range. The secondary efficacy endpoints were serum concentrations and PK parameters of total T, free T, and DHT, in addition to patient and investigator ratings of acceptability and preference for this product. Statistical analyses consisted of analysis of treatment responders in terms of C_{avg} and PK parameters, in addition to descriptive statistics. In total, 84 patients completed the study. Reasons for discontinuation were: patient request for withdrawal (n=10), protocol violation (n=2), patient withdrawal by investigator (n=1), and 1 death in a motor vehicle accident. Mean age was 53.6 years, mean weight was 92.2 kg, and mean height was 177.8 cm. Approximately 10% were current users of oral tobacco, approximately 42% were current alcohol drinkers, and 69.4% were Caucasian. There were 72% primary efficacy responders (95% CI: 61-81%) and 87% supplemental efficacy responders (95% CI: 77-93%). In responders at Week 12, the $C_{max(0-24)}$ was 9.96 ng/ml, $C_{min(0-24)}$ was 3.15 ng/ml, and $T_{max(0-24)}$ was 11.8 hours. The mean percentage of time over the 24 hour sampling period that T levels were in the normal range was 89%. In supplemental efficacy responders the mean $C_{avg(0-24)}$ was 5.4 ng/ml.

COL-1621-07 was a smaller Phase 3 randomized, open-label, parallel-arm, multi-center study of the efficacy and safety of Striant® applied twice-daily compared with a registered dermal patch containing 5 mg of testosterone applied once daily. The primary efficacy endpoint was to determine the non-inferiority of the buccal system to the dermal patch during applications for 7 consecutive days. The secondary efficacy endpoints were the percentage of patients with total T outside of the normal range at end of study, and the comparison of T

and DHT ratios. A total of 67 patients were randomized (1 discontinued because of an AE), with similar demographics between the groups. Mean age was approximately 50, over 90% were Caucasian, approximately 20% were current smokers, and 88% drank alcohol. Mean weight was approximately 85 kg, mean height 177 cm, and mean BMI was approximately 27 kg/m². The mean time-averaged total T for the buccal and dermal products were respectively: $C_{avg(0-12)}$ 5.98 and 3.67 ng/ml, and $C_{avg(12-24)}$ 4.99 and 3.68 ng/ml. These results indicate that, in this small trial, in terms of mean T levels, the buccal product was at least comparable (and perhaps superior) to the dermal product. In addition, for the buccal product, mean total T at all time points were within the normal range, and steady-state was achieved within 3 days.

COL-1621-04 was a Phase 2, open-label, single center study to investigate the long-term safety and efficacy of Striant® applied twice daily in 12 hypogonadal men for 12 consecutive weeks. The primary efficacy endpoints were total T levels and percentage of total T in the normal range. The secondary efficacy end points were the free T index, DHT levels, and T/DHT ratios. In total, 12 white patients enrolled and completed the study. Ages were 26-61 (mean 47.1), mean weight was 95.6 kg, and mean height was 175.8 cm. One patient had primary hyogonadism and 11 had secondary hypogonadism. In all patients, total T was in the normal range at most time points, and at follow-up for all patients. The mean total T at each time point during treatment ranged from 4.5-7.4 ng/ml, and the mean average total T over all visits during treatment was 5.6 ng/ml.

COL-1621-03 was a Phase-1, open-label, single center study to investigate the PK profile of Striant® in 12 patients (ages 26-61) following twice daily applications for 7 days. Efficacy endpoints were serum levels and PK parameters of total T, free T, and DTH. During the 7-day application period, steady-state was achieved within the first 24 hours, and mean serum T remained between 4.43 and 7.21 ng/ml.

COL-1621-08, -09, and -10 are currently ongoing studies with data from safety updates included below in Section 7.4 b of this review. Detailed safety data review can be found in the Appendix.

**APPEARS THIS WAY
ON ORIGINAL**

COL-1621-08 is an open-label, Phase-3, multicenter study (being conducted in England) of Striant® for long-term (12-month) safety and efficacy in T deficient men. The study is still ongoing, with an expected final study report by _____. Expected enrollment is 200 patients in 20 centers. Inclusion criteria are: ages 18-74, BMI \leq 35, and serum T $<$ 2 ng/mL. Exclusion criteria are: BPH with AUA symptom score \geq 20, history or suspicion of prostate cancer, PSA above normal for the core laboratory, HCT $>$ 50, use of corticosteroids in amounts $>$ 40 mg daily of hydrocortisone or equivalent, use of unlicensed drug within 30 days of study entry, and evidence of drug or alcohol abuse. The primary efficacy endpoint is the percentage of timepoints in which serum T is in the normal range. Secondary endpoints are DHT levels, T/DHT ratios, lipid profile, and safety data in terms of AE's. Efficacy data are not currently available, and available safety data (only AE and gum check data) on 27 patients is incorporated into the 4-month safety update in Section 7.4 b, and Table 7 of this review.

COL-1621-09 is similar to that of COL-1621-08 except that it is being conducted at 13 centers in the US. Recruitment is complete with 162 patients enrolled. Inclusion criteria are: ages 18-79, BMI \leq 35, and serum T $<$ 2.5 ng/mL. Exclusion criteria are: BPH with AUA symptom score \geq 20, history or suspicion of prostate cancer, PSA $>$ 4 ng/mL (age $>$ 39), PSA $>$ 2.5 ng/mL (age $<$ 40), HIV positive, HCT $>$ 52, evidence of drug or alcohol abuse, received investigational drugs within 30 days of study. This study is currently ongoing with the final report expected in _____. The safety and efficacy endpoints are the same as in COL-1621-08, above. The safety data from 97 patients with 6-month exposure and 38 patients with 12-month exposure are incorporated into the 4-month safety update in Section 7.4 b, and Table 7 of this review.

COL-1621-10 is a Phase-3, randomized, open-label, parallel arm, multicenter, 14 day study of the safety and efficacy of Striant® compared with Androgel® (5 g) in testosterone deficient men. Patient recruitment is complete and 13 patients were randomized to the buccal group. The inclusion and exclusion criteria as well as the safety and efficacy endpoints were exactly the same as in COL-1621-08. The study objectives were to describe the steady-state of the 2 preparations with regard serum T during the 24-hour period on the last day of dosing, to summarize the serum T levels at steady-state, and to assess the safety profiles. Efficacy data are not currently available. The safety update data from the 13 patients randomized to the buccal group has been incorporated into Table 7 of this review.

6.4 Efficacy Conclusion.

The 2 pivotal Phase-3 studies and 5 additional supporting open-label clinical trials have demonstrated that Striant® applied twice daily for periods up to 12 months in hypogonadal men can attain and maintain serum T levels within the physiological range.

Reviewer's Comment: In addition to demonstrating satisfactory efficacy as replacement therapy in hypogonadal men, the efficacy of this buccal product was at least comparable (non-inferior) to that of the available replacement product. However, this comparative study was performed in relatively few patients and valid claims cannot be supported from such a limited sample.

7. Integrated Review of Safety.

7.1 Brief Statement of Findings.

Safety variables assessed included: clinical AE's, gum checks, hematology/clinical chemistry, serum hormones, vital signs, and ECG's. The most commonly reported treatment related AE's were: application site reaction (11.8%), upper respiratory infections (6.3%), headache (5.6%), and dysgeusia (4.8%).

7.2 Materials Used in Review.

Adverse events (AE's) data were derived from the 4 trials cited above (as described in the Integrated Review of Efficacy above) and from two other Phase 3, open-label, long-term (12-month) trials involving an additional 165 patients in the safety population, which now totals 323.

7.3 Extent of Exposure.

In all studies, patients received a 30 mg buccal system applied twice daily. The duration of exposure is seen in Table 6.

Table 6: Extent of Exposure

Study No.	Duration of Treatment	No. in Safety Population
COL-1621-03	7 days	12
COL-1621-07	7 days	33
COL-1621-10	14 days	13
COL-1621-04	12 weeks	12
COL-1621-05	12 weeks	98
COL- 1621-08	12 months	27
COL-1621-09	12 months	138

7.4 Summary of Safety Findings.

a) Clinical Safety Data.

The safety variables assessed in the clinical trials were: clinical AE's, gum examinations, laboratory parameters (hematology, urinalysis, clinical chemistry, and hormone assays), vital signs, and ECG's.

Data from the 4 short-term PK studies using the Striant® formulation in 18 female volunteers and 24 hypogonadal men indicated a total of 5 treatment-related AE's (2 gum and 3 mouth-related AE's).

The other short-term study involved 33 hypogonadal men. In this study, there were 28 reported AE's in 17 patients. Of these 42% were judged as mild, 9% as moderate, and none as severe. The AE's included: dysgeusia, application site reactions, viral upper respiratory infections and headaches (3 events were regarded as probably drug-related, and 9 events as possibly drug-related).

In the 2 three-month clinical studies (total of 110 patients), the most frequently reported AE's were; application site irritation (9.1%), dysgeusia (3.6%), headache (3.6%), application site pain, sore throat, fatigue, and upper respiratory infection (each at 2.7%). Interim data from the 2 long-term (12-month) studies indicate no reported application site reactions, and the most commonly reported AE's being: upper respiratory infection, hypertension, and nausea.

The most common drug related AE's in the 7-day and 3-month studies were application site and taste disorders. In the long-term studies, increased hematocrit (2.1%) was the most common treatment-related AE.

b) Safety Update.

In this 4-month safety update, safety data has become available on additional patients from 1 completed 14-day study and 2 ongoing 12-month studies. There were 199 patients in the safety population, including 117 patients with at least 6 months of drug exposure (51 of whom have had 12-months exposure). This update includes only gum examination and clinical AE data. An overall summary of the AE update is seen in Table 7.

Table 7: AE Update Summary (safety population)

Exposure	14 days (N=13)	6 months (N=117)	12 months (N=51)
No. with any AE	6 (46%)	43 (37%)	15 (29%)
Mild Intensity	4 (31%)	17 (15%)	6 (12%)
Moderate Intensity	2 (15%)	21 (18%)	8 (16%)
Severe Intensity	0	5 (4%)	1 (2%)
Related to Drug	0	5 (4%)	0
Not Drug-Related	4 (31%)	21 (18%)	8 (16%)
Probably-Related	0	7 (6%)	2 (4%)
Possibly-Related	1 (8%)	8 (7%)	3 (6%)

Reviewer's Comment: The majority of the clinical AE's were regarded as being unrelated to the study drug, and appeared to be independent of the extent of exposure (7 days versus 12 months). The most frequent study drug related AE's were application site and mouth reactions, which were relatively rare (4%), generally of mild to moderate intensity, and reversible. In addition, the 51 patients with 12 months of drug exposure fulfilled the sponsor's commitment to the Division, agreed upon at the Pre-NDA meeting.

8.0 Dosing, Regimen, and Administration Issues.

The dose used in these clinical trials was derived from two Phase-1 studies in healthy male volunteers and three Phase- 2 studies in hypogonadal men. The 30 mg dose and regimen appeared to have the best balance between safety and efficacy in achieving stable physiological levels of serum T. Tolerability was generally acceptable.

9.0 Use in Special Populations.

Gender: Striant® is indicated for replacement therapy of testosterone in hypogonadal men. It should not be used in women.

Pediatric: The sponsor had requested to defer a pediatric study until such time as they receive approval for the adult indication, and the Division agreed with that request.

Elderly: The inclusion criteria for the study populations in the clinical efficacy studies were hypogonadal men ages 18-80. There are no data to suggest concern using this product in the elderly.

Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of this product has not been studied. However, the pivotal Phase 3 study did include approximately 10% African-American patients

Renal or Hepatic Insufficiency: No pharmacokinetic studies were conducted in patients with renal or hepatic compromise.

10.0 Conclusions, Recommendations, and Labeling.

10.1. Conclusions Regarding Safety and Efficacy.

It can be concluded that the safety and efficacy of Striant® has been established for replacement of testosterone in hypogonadal men.

10.2. Recommendations on Approvability.

From a clinical perspective, Striant® should be approved for the indication "testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone".

10.3. Labeling.

Review of the draft package insert indicates that for clinical parameters it is essentially the same as that for the currently marketed Testosterone Gel and the Testosterone Transdermal Systems proposed for the same indications.

11. Appendix

A. Clinical Efficacy and Safety Studies (in further detail):

COL-1621-03 was a Phase-1, open-label, single center study of the pharmacokinetics and tolerability of Striant® applied every 12 hours for 7 days in 12 testosterone deficient men (T level < 2.5 ng/ml, ages 26-61, and BMI < 35 kg/m²). Major exclusion criteria were: current use of a corticosteroid or other unapproved drug, moderate or severe symptoms of

BPH, PSA > 2.5µg/L (age < 50) or > 4.5µg/L (ages 50-65), and history or suspicion of prostate cancer. PK data can be found above in Section 3, Table 5 of this review. Testosterone and DTH levels were assayed in serum and urine by validated enzyme and radioimmuno-assays. This study indicated that steady-state T levels in the physiological range for healthy men (3.1-9.8 ng/mL) were achieved after approximately 24 hours of initiating product use, and was generally well tolerated. Fourteen hours after the application of the final tablet, the average serum total T decreased to 3.02 ng/mL, and at 24 hours post-application, the mean serum T fell to 0.99 ng/mL. There were no deaths, serious AE's or other significant AE's reported during the study. There was 1 treatment-related AE (headache), and 1 case of mild gingivitis, considered by the investigator to be unrelated to the study product. In addition to medical history and physical examinations (including gum inspections) to assess adverse events, variables measured to monitor safety included hematology, clinical biochemistry, urinalyses, a 12-lead ECG, and vital signs. Eight of 12 patients reported difficulty getting the product to stick to the gum, and 9 patients had to replace 1 or more systems(s).

COL-1621-04 was a Phase-2, open-label, single-center study of Striant® applied twice daily for 12 weeks in 12 testosterone-deficient men who had participated in previous studies COL-1621-02 or 03, with the same inclusion and exclusion criteria described in the preceding paragraph. The primary efficacy endpoints were total T serum concentration and percentage of total T concentrations within normal range. Safety endpoints included physical examinations, AE's, clinical chemistry, hematology, and urinalyses, vital signs, and a 12-lead ECG. Patient characteristics and efficacy results are summarized above in Section 6.3 of this review. Total T concentrations during treatment were within the normal range (3.0-10.5 ng/mL) at most time points in all patients, with a mean total T ranging from 4.52-7.38 ng/mL. The overall mean serum T over all visits during treatment was 5.64 ng/mL. At baseline, only 1 patient (8.3%) had normal total T concentration. During treatment between 5 (41.7% and 11 (91.7%) patients had normal T at any assessment point. At follow-up (after stopping dosing) no patient had normal T. Ten of 71 assessments (14.1%) during treatment were below the normal T level in 7 (58.3%) patients, and 5 of 71 (7.0%) assessments were above the normal in 4 patients (33.3%). No serious AE's or AE's leading to study discontinuation were reported. Four patients reported 4 clinical AE's of mild to moderate intensity (back discomfort, hypertension, emotional lability, and respiratory tract infection). Only the emotional lability was regarded as being possibly related to study drug, and continued through the end of the 42 days follow-up. Two patients had low-to-normal shift in RBC count, and 3 had low-to-normal shift in hemoglobin and HCT. These were regarded as expected secondary to androgen-related increased erythropoietic activity. One patient had a WBC count that was slightly below the normal range, which was not considered clinically significant. At follow-up, normal-to-high shifts in liver enzymes from baseline were seen in 4 patients, including AST and ALT in 3 patients, and GGTT in 1 patient. Similar shifts were seen for glucose in 2 patients and cholesterol in 1 patient. Except for 1 patient (a diabetic with abnormal GGT and glucose levels at both baseline and follow-up), the investigator did not regard any other abnormal chemistry results as clinically significant. There were no deaths, serious AE's or clinical AE of severe intensity reported in the study.

COL-1621-05 was a pivotal Phase-3, open-label, single-arm, multi-center evaluation of the efficacy and tolerability of Striant® following twice daily repeated dosing for 12 consecutive weeks in 98 hypogonadal men. Key inclusion criteria were: ages 18-80, serum T < 2.5 ng/ml, Body Mass Index (BMI) \leq 35 kg/m², and adequate washout of any previous T replacement therapy. The primary efficacy endpoint was the percentage of responders having time-averaged-steady-state total T levels ($C_{avg\ 0-12}$ and $C_{avg\ 12-24}$) over the last 2 consecutive 12-hour dosing intervals within the physiological range and \geq 3.0 ng/ml at week 12. Supplemental primary efficacy endpoint responders were defined as those having the last 2 consecutive 12-hour dosing intervals ($C_{avg\ 0-24}$) within the physiological range. The secondary efficacy endpoints were serum concentrations and PK parameters of total T, free T, and DHT, in addition to patient and investigator ratings of acceptability and preference for this product. Statistical analyses consisted of analysis of treatment responders in terms of C_{avg} and other PK parameters, in addition to descriptive statistics. In total, 84 patients completed the study. Reasons for discontinuation were: patient request for withdrawal (n=10), protocol violation (n=2), patient withdrawal by investigator (n=1), and 1 death in a motor vehicle accident. Mean age was 53.6 years, mean weight was 92.2 kg, and mean height was 177.8 cm. Approximately 10% were current users of oral tobacco, approximately 42% were current alcohol drinkers, and 69.4% were Caucasian. There were 72% primary efficacy responders (95% CI: 61-81%) and 87% supplemental efficacy responders (95% CI: 77-93%). In responders at Week 12, the $C_{max(0-24)}$ was 9.96 ng/ml, $C_{min(0-24)}$ was 3.15 ng/ml, and $T_{max(0-24)}$ was 11.8 hours. The mean percentage of time over the 24 hour sampling period that T levels were in the normal range was 89%. In supplemental efficacy responders the mean $C_{avg(0-24)}$ was 5.4 ng/ml. Tolerability and safety endpoints were gum examinations, AE's, hematology, clinical chemistry, urinalyses, SHBG, LH, FSH, E₂, vital signs, and ECG. Overall, 55 patients (56.1%) reported 116 AE's. Most common AE's were application site disorders (15.3%), body as a whole (13.3%), and respiratory disorders (11.2%). The majority of AE's were mild or moderate, with only 8.2% reported as severe. AE's of severe intensity were application site irritation (2 patients), hyperkalemia, kidney stone, fatigue, limb pain, and motor vehicle death (each reported by 1 patient). With the exception of application site irritation in 7 patients and dysgeusia in 3 patients, other AE's regarded as related to study drug occurred in only 1 or 2 patients. Other than gum-related AE's, the most common AE's reported by 2 or more patients were headache (4), and fatigue, respiratory infection, and sore throat (each in 3 patients). Reported serious AE's were auto accident death, hyperkalemia and pneumonia, all considered to be unrelated to study drug. In addition to the 1 death, there were 4 discontinuations from the study, 2 with mouth disorders and 2 with gum irritations. Gum abnormalities (mostly gingivitis or edema) were more common at baseline and follow-up than during treatment. Laboratory findings were generally unremarkable. The most frequently reported AE's by body system and preferred term can be seen in Table 8 below.

Table 8. Most Frequent AE's ($\geq 2\%$) Study COL-1621-05 (N=98)	n (%)
All body systems	55 (56.1%)
Application site disorders	15 (15.3%)
Application site irritation	10 (10.2%)
Application site pain	3 (3.1%)
Application site edema	2 (2.1%)
Body as a whole	13 (13.3%)
Fatigue	3 (3.1%)
Allergy	2 (2.0%)
Respiratory system disorder	11 (11.2%)
Sore throat	3 (3.1%)
Upper respiratory tract infection	3 (3.1%)
Gastrointestinal system disorders	9 (9.2%)
Gingivitis	2 (2.0%)
Tooth ache	2 (2.0%)
Other special senses disorders	7 (7.1%)
Bitter taste	4 (4.1%)
Dysgeusia	2 (2.0%)
Musculoskeletal disorders	5 (5.1%)
Joint pain	2 (2.0%)
Psychiatric disorders	3 (3.1%)
Red blood cell disorders	3 (3.1%)
Hematocrit increased	2 (2.0%)
Skin and appendages disorders	3 (3.1%)
Resistance mechanism disorders	2 (2.0%)
Infection localized	2 (2.0%)
Secondary terms	2 (2.0%)
Urinary system disorders	2 (2.0%)
Vision disorders	2 (2.0%)

COL-1621-07 was a smaller, Phase-3, randomized, open-label, parallel arm, multi-center study of the efficacy and safety of Striant® compared with a registered dermal patch - containing 5 mg of testosterone applied once daily. The primary efficacy endpoint was to determine the non-inferiority of the buccal product to the dermal patch product during applications for 7 consecutive days. The secondary efficacy endpoints were the percentage of patients with total T outside of the normal range at end of study, and the comparison of T and DTH ratios. A total of 67 patients were randomized. In the buccal group, 1 patient was withdrawn from the study because of an AE on Day 3 related to gum tenderness and the development of a gum blister. Demographics were similar between the groups. Mean age was approximately 50 years, over 90% of patients were Caucasian, approximately 20% were current smokers, and 88% drank alcohol. Mean weight was approximately 85 kg, mean height was 177 cm, and mean BMI was approximately 27 kg/m². The mean time-averaged total T for the buccal and dermal products were respectively: C_{avg}(0-12) 5.98 and 3.67 ng/ml, and C_{avg}(12-24) 4.99 and 3.68 ng/ml. These

results indicate that, in terms of mean T levels, the buccal product was at least comparable to the dermal product. In addition, for the buccal product, mean total T at all time points was within the normal range, and steady-state was achieved within 3 days. Mean free T index increased in both treatment groups from baseline (from 15.8 to between 67.8 and 97.2 in the buccal group, and from 25.9 to between 34.7 and 58.9 in the dermal group). All mean T concentrations for both cohorts were within the physiological range and the magnitude and shape of the concentration-time curves were similar. Safety endpoints for the buccal population (33 patients) included clinical AE's, gum checks, serum hormones and SHBG, clinical chemistry, hematology, and urinalyses, vital signs, and a 12-lead ECG. The buccal group reported a total of 28 mild AE's in 17 patients (51.5%). The most common AE was application site disorder reported by 6 patients (18.2%). Twelve patients (36.4%) in the buccal group had AE's regarded as possibly or probably related to study drug, and only 2 patients (6.1%) developed gum abnormalities from baseline to follow-up. There were no clinically significant changes in any of the other monitored safety endpoints from baseline to follow-up. There were no serious AE's reported and no patient died. The most frequently reported AE's by body system and preferred terms in the safety population can be seen in Table 9 below.

Table 9. Most Frequent AE's ($\geq 3\%$) Study COL-1621-07 (N=33)

	n (%)
All body systems	17 (51.5%)
Application site disorders	6 (18.2%)
Application site irritation	2 (6.1%)
Application site pain	1 (3.0%)
Application site erythema	2 (6.1%)
Application site reaction	1 (3.0%)
Secondary terms-events	1 (3.0%)
Medication error	1 (3.0%)
Body as a whole	1 (3.0%)
Hot flashes	1 (3.0%)
Resistance mechanism disorders	1 (3.0%)
Herpes simplex	1 (3.0%)
Central and peripheral nervous system disorders	4 (12.1%)
Dizziness	1 (3.0%)
Faintness	1 (3.0%)
Headache	2 (6.1%)
Skin and appendage disorders	1 (3.0%)
Acne	1 (3.0%)
Respiratory system disorder	2 (6.1%)
Viral upper respiratory tract infection	2 (6.1%)
Gastrointestinal system disorders	9 (9.2%)
Belching	1 (3.0%)

Nausea	1 (3.0%)
Vomiting	1 (3.0%)
Other special senses disorders	3 (9.1%)
Dysgeusia	3 (9.1%)
Musculoskeletal disorders	1 (3.0%)
Muscle pain	1 (3.0%)
Liver and biliary system disorders	1 (3.0%)
ALAT increased	1 (3.0%)

COL-1621-08 is an ongoing, open-label, Phase-3, multi-center study (being conducted in England) of Striant® for long-term (12-month) safety and efficacy in T deficient men. The study is still ongoing, with an expected final study report by the . Expected enrollment is 200 patients in 20 centers. Major inclusion criteria are: ages 18-74, BMI \leq 35, and serum T < 2 ng/mL. Major exclusion criteria are: BPH with AUA symptom score \geq 20, history or suspicion of prostate cancer, PSA above normal for core laboratory, HCT > 50, use of corticosteroids in amounts > 40 mg daily of hydrocortisone or equivalent, use of unlicensed drug within 30 days of study entry, and evidence of drug or alcohol abuse. The primary efficacy endpoint is the percentage of timepoints in which serum T is in the normal range. Secondary endpoints are DHT levels, T/DHT ratios, lipid profile, and safety data in terms of clinical AE's. Efficacy data are not currently available, and available safety data (clinical AE and gum check data) on 27 patients is incorporated into the 4-month safety update in section 7.4 b, and Table 7 of this review. In the safety population of 33 patients with 6 to 12 months exposure there were 2 reports each of flu-like symptoms, skin hyperpigmentation, and sticky eye, and one each of the following: vomiting, upper respiratory infection, dry mouth, palpitations aggravated, pneumonia, leg pain, and localized numbness.

COL-1621-09 is similar to that of COL-1621-08 except that it is being conducted at 13 centers in the US. Recruitment is complete with 162 patients enrolled. Major inclusion criteria are: ages 18-79, BMI \leq 35, and serum T < 2.5 ng/mL. Major exclusion criteria are: BPH with AUA symptom score \geq 20, history or suspicion of prostate cancer, PSA > 4 ng/mL (age > 39), PSA > 2.5 ng/mL (age < 40), HIV positive, HCT > 52, evidence of drug or alcohol abuse, received investigational drugs within 30 days of study. This study is currently ongoing with the final report expected . The safety and efficacy endpoints are the same as in COL-1621-08, above. The safety data from 97 patients with 6-month exposure and 38 patients with 12-month exposure are incorporated into the 4-month safety update in section 7.4 b, and Table 7 of this review. In the safety population of 135 patients, there were 6 reports of infection, 4 reports each of anxiety, nausea, and depression, 3 reports each of hypertension and polycythemia, 2 reports each of hyperlipidemia, gingivitis, rising PSA, bronchitis, and abdominal pain; and 1 each of insomnia, arthralgia, abnormal triglycerides, tinnitus, upper respiratory infection, urinary tract infection, vomiting, joint ache, myalgia, paralysis, pneumonia, pulmonary congestion, abnormal renal function, aggravated diabetes, dizziness, atrial fibrillation, and aggravated hypertension.

COL-1621-10 is a Phase-3, randomized, open-label, parallel arm, multi-center, 14-day study of the safety and efficacy of Striant® compared with Androgel® (5 gm) in testosterone-deficient men. Patient recruitment is complete and 13 patients were randomized to the buccal group. The inclusion and exclusion criteria as well as the safety and efficacy endpoints were exactly the same as in COL-1621-08. The study objectives were to describe the steady-state of the 2 preparations with regard serum T during the 24-hour period on the last day of dosing, to summarize the serum T levels at steady-state, and to assess the safety profiles. Efficacy data are not currently available. The safety update data from the 13 patients randomized to the buccal group has been incorporated into Table 7 above. The reported AE's, one patient each, were: accident (non-specific), acne, anemia, cough, headache, hematuria, HDL decrease, and rhinitis. Headache was the only AE regarded as related to the study drug. Cough and rhinitis were deemed not assessable (relationship could not be determined). No patient in the buccal group reported a gum, mouth, or taste-related AE.

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

/s/

Harry Handelsman
6/12/03 11:01:47 AM
MEDICAL OFFICER

Mark S. Hirsch
6/12/03 12:12:42 PM
MEDICAL OFFICER
I concur.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

DATE: February 24, 2003

FROM: Fred Hyman, D.D.S. M.P.H, Dental Officer, HFD-540

THROUGH: John Kelsey, D.D.S., M.B.A., Dental Team Leader, HFD-540

THROUGH: Jonathan Wilkin, M.D., Division Director, HFD-540

TO: Eufrecina Deguia, Project Manager, HFD-580

SUBJECT: Consult to the Division of Reproductive and Urologic Drug Products,
HFD-580 for NDA 21-543, Striant (Testosterone Buccal Bioadhesive)

HFD-540 Consult #414

Introduction and Regulatory Background

Testosterone replacement therapy has been shown to be effective in men suffering from either primary or secondary hypogonadism. Although testosterone replacement therapy is available in different formulations, there is still a need for a user-friendly delivery system that can provide the normal physiological levels of testosterone in men. Approved routes of administration for testosterone include I.M. injections, transdermal patches, and topically applied gel. Oral administration of testosterone has not been successful as it is extensively metabolized through the hepatic first-pass metabolism. Striant, the subject of this NDA, is a bioadhesive buccal tablet containing 30-mg testosterone. Because venous drainage from the mouth is to the superior vena cava, transbuccal mucosal delivery of testosterone substantially circumvents first-pass metabolism and therefore, seems to be a rational method of testosterone delivery. The studies that were conducted under the IND for Striant examined its safety, efficacy, and acceptability in testosterone deficient men.

The IND associated with this drug, 60,906, was opened on August 30, 2000. At that time, the Division of Reproductive and Urologic Drug Products (HFD-580) requested via formal consult that HFD-540 review a proposed protocol for a phase 3 study, and provide comments about the patch's potential effects on the oral cavity. HFD-540 staff provided comments including a recommendation for including more frequent examination of the application site and more specific questions about emergent adverse oral events, and a suggestion that the patch be varied in its placement to minimize the potential for irritation. These comments were relayed to the sponsor through HFD-580 project management on October 3, 2000. There is no documentation of an End-of-Phase 2 meeting with the Agency for this drug. However, on December 5, 2001, HFD-580 hosted a Pre-NDA meeting with the sponsor, during which several agreements were made. There was no representation from HFD-540 at that meeting.

This NDA was submitted to HFD-580 on August 20, 2002, and contains results of eight completed studies. Two open label studies were still underway at the time of submission. The pivotal trials enrolled testosterone deficient men with the primary outcome variable being achievement of testosterone levels within the normal physiologic range. Adverse events (AE's) were monitored, including oral examinations at the site of the patch placement. During the pre-NDA meeting, HFD-580 agreed to accept follow-up results from the open label studies, as long as the Agency received the final study reports at the 4-Month Safety Update.

Requested Information in the Current Consult:

In correspondence dated February 19, 2003, HFD-580 requested a consult from the Dental Team in HFD-540 to review the NDA for the following: "Please give us your opinion regarding the issue of buccal irritation and the induction or promotion of localized squamous cell carcinoma." Supplied with the consult request were photocopies of pertinent tables and results sections from the sponsor's NDA submission, and a compact disc from the sponsor containing study reports from completed trials.

In the remainder of this consult, an overview of the trials will be described along with comments about possible shortcomings or omissions from an oral health viewpoint. A

review of literature will also be provided to address the potential for induction or promotion of localized squamous cell carcinoma. Please note that it is not the intent of this consult to provide recommendations for regulatory action regarding this drug. The regulatory decision will need to be made by HFD-580.

Summary of NDA Submission

The submission contains results of eight completed studies, which include five phase 1 studies, one phase 2 study, and three phase 3 studies. Partial results from 2 ongoing one-year open-label safety studies have been submitted as well in response to HFD-580's request for 6-month and 12-month safety data. In three of the initial phase 1 studies, healthy females, rather than males were chosen – this was done to help establish the proper dosing by avoiding interference with the circadian rhythm of endogenous testosterone normally seen in young healthy males. The sponsor next enrolled a small number of testosterone deficient men, in one trial as a single dose, and in another trial for 7 days of dosing. Next the sponsor conducted a phase 2 trial in testosterone deficient men for 12 weeks, and finally two phase 3 trials. In one of the phase 3 trials, 80 testosterone deficient men were randomly assigned for 7 days to either an approved testosterone skin patch or to the Striant and the results were compared. In the other phase 3 trial, 98 testosterone deficient men were assigned to Striant for 12 weeks. Note that neither phase 3 trial was placebo controlled; because the outcome was serum levels of testosterone and its metabolites, HFD-580 agreed that blinding was not necessary. The consequence of omitting a placebo for AE monitoring is discussed later in this review.

For ease of following the progression of the trials and the meaning of any AEs uncovered, a table has been created that summarizes the phase, size, duration, results and reported oral AEs associated with each trial.

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Phase	Study ID	Subjects	Duration	Summary	Adverse Events Oral
1	COL 1621-ISO1	22 healthy females	Single dose	A single dose of the drug raised serum testosterone concentrations up to levels that were within the normal reference range for healthy young males. The safety profile was favorable.	One subject reported bitter taste and powder residue in mouth.
1	COL 1621-GB01	10 healthy females	Single dose	A single dose of Striant showed blood levels of testosterone as expected within the physiological range seen in normal healthy males.	Erythema of the gum at the site of application was noted following removal of the tablet after 12 hours.
1	COL 1621-06	9 healthy females	Single dose	A single dose of Striant demonstrated testosterone levels that were within a normal range for healthy males. In this trial, "gum checks" were performed at 30 minutes, 24 hours and 36 hours after drug administration, and all subjects were examined at a post-dose follow-up exam at 30 days.	None reported.
1	COL 1621-02	12 testosterone deficient men	Single dose	In this randomized, double blind, placebo-controlled crossover study, subjects received either placebo or Striant for one dose. After the wash out period of 48 hours, subjects were crossed over to receive the other test product. Mean serum testosterone (total) concentration in subjects reached the physiologic range when they received the Striant, whereas it did not when they were assigned the placebo.	One subject reported mild gum soreness
1	COL 1621-03	12 testosterone deficient men	7 days	Twice daily administration of Striant for 7 consecutive days resulted in mean serum total testosterone concentrations within physiological range for healthy men. Steady state serum testosterone levels were achieved within 24 hours after starting treatment.	One adverse event of mild gingivitis was reported.
2	COL 1621-04	12 testosterone deficient men	12 weeks	Subjects for this trial were recruited from the single dose trials COL1621-02 and 03. Striant tablets were applied twice daily for 12 weeks. Results showed normal levels of testosterone during the 12 weeks.	None reported
3	COL 1621-05	98 testosterone deficient men were enrolled (84 completed).	12 weeks	<p>The percentage of treatment responders was high. Overall, 72% of patients were classified as primary efficacy responders, which is based on $C_{avg(0-12)}$ and $C_{avg(12-24)}$ within the normal range (3.0 to 10.5 ng/ml) and $C_{12/24(avg)} \geq 3.0$ ng/ml. In addition, 87% of patients were classified as supplemental efficacy responders, which is based on $C_{avg(0-24)}$ within the normal range.</p> <p>The high percentage of responders is supported by the secondary efficacy results, which demonstrated ideal PK characteristics of COL-1621. Total testosterone, free testosterone, and DHT concentrations were consistently sustained within their respective normal range. Post-hoc exploratory analysis showed that the PK of COL-1621 was not affected by BMI, food and beverage, gum abnormalities, or medications that can potentially cause dry mouth.</p>	A total of 16 patients (16.3%) reported 19 gum-related AEs. Onset of most gum-related AEs was in the first month of treatment and, with the exception of 2 AEs of mild intensity, all AEs resolved in ≤ 11 days. There were 5 patient discontinuations from the study due to AEs. Two patients had gum irritation, 1 patient had mouth irritation, and 1 patient experienced bad taste in the mouth. All AEs leading to patient discontinuation from the study resolved in 8 days or less, with the exception of mouth irritation for which duration is unknown. Gum abnormalities on gum examination were up to 3 times more common at Baseline or Follow-up when the patient was not taking study drug, than during the treatment period. The majority of gum abnormalities were gingivitis or edema, and either continued unchanged throughout the study, or resolved. No cases of leukoplakia or ulcerations were observed. None of the gum abnormalities were considered to be severe and most were reported as mild in intensity
3	COL 1621-07	80 testosterone deficient men; 40 received Andropatch, 40 received Striant	7 days	Subjects were assigned to either Striant or a marketed testosterone patch in a parallel group design. Striant was found to be at least as good as Andropatch in the non-inferiority analysis. With subjects on Striant more likely to have total testosterone concentrations within the physiologic range than patients receiving Andropatch. Gum checks were performed only on the Striant group, at visit one and follow-up (within 2 weeks of final dosing)	Two subjects developed erythema at the application site, two developed application site irritation. One subject reported application site pain and blistering, and difficulty with the patch sticking. That subject withdrew from the study due to those problems.

Method for Monitoring Oral Events

In order to monitor the oral effects and uncover any signs of oral irritation or pathology, the sponsor included oral examinations in all of their trials except one phase 2 study, COL 1621-04. The sponsor employed a procedure they referred to as a "gum check", but provided no detail. In COL 1621-03, checks were performed during treatment and at follow-up; in COL 1621-07, assessments were made at baseline and follow-up only. In those two studies, it was only noted whether or not the gum check was normal. In COL 1621-05, gum checks were performed at baseline, follow-up, and monthly during treatment. In long-term safety studies COL 1621-08 and COL 1621-09, gum checks were performed every 3 months. If deemed abnormal, the investigator supplied details on gingivitis, edema, ulceration, lesions and leukoplakia. Each abnormality was rated as absent, mild, moderate or severe.

Adverse Events Results

Refer to the table earlier in this review for details on the oral AEs of all studies with the exception of the ongoing safety studies COL 1621-08 and COL 1621-09, which were submitted separately at the four-month safety update. The majority of gum abnormalities were reported as gingivitis or edema, and either continued unchanged throughout the study, or resolved. No cases of leukoplakia or ulcerations were observed. None of the gum abnormalities were considered to be severe and most were reported as mild in intensity. In the largest study, COL 1621-05, 32 subjects or 33% were identified as having mild or moderate gingivitis at baseline. At each of the three gum checks conducted during the study (week 4, 8 and 12), the reports of gingivitis actually decreased to 10 (10%) at week 4 and 8 and 11 (11%) at week 12. At follow-up, the reported incidence of gingivitis increased to 19 (19%). See the discussion section of this consult for comments on why gingival abnormalities were up to 3 times more common at Baseline or Follow-up when the patient was not taking study drug, than during the treatment period.

In the two open label studies, Study COL 1621-08 and COL 1621-09, the incidence of AE's was much lower than the earlier studies. In study COL 1621-08, there were zero reports during the 12 months duration of gingivitis (mild, moderate, or severe), edema, ulcerations, or other lesions. In study COL 1621-09, there were reports of 4 subjects with gingivitis at baseline (10.5%) and 2 subjects who had gum abnormalities at the 12-month exam (5.2%).

Discussion:

Testosterone has been well-studied in humans and animals – what makes Striant unique is its novel delivery system. Since all of the subjects in the pivotal clinical trials are testosterone deficient, restoring the levels to the physiologic norm is the goal of this treatment. The primary outcome variable in pivotal trial COL 1621-05 is the percentage of subjects who achieved normal physiologic levels of serum testosterone, based upon reference standards. In the other pivotal trial, COL 1621-07, the primary outcome variable is the percentage of subjects on Striant in the normal physiologic range, compared to the percentage of subjects in the normal physiologic range who were using an approved dermal delivery form of testosterone. Clinical symptoms related to restoration of normal testosterone levels are not solicited or measured. Although the safety profile will look at all reported AE's, HFD-580's "main safety concern is gum

irritation and gum related adverse events." (End-of-Phase 2 Meeting minutes 12-05-2001).

Rationale for Monitoring Oral Events

In each of the trials, the subjects were instructed to place one tablet above the right or left incisor tooth with the rounded side against the gum. In addition, in both phase 3 trials and in long-term safety studies COL 1621-08 and COL 1621-09, subjects were instructed to alternate placement of the patch between the right and left sites with each application. In order to adequately review the safety of this product, the question of oral irritation must be examined. There are several reasons to suspect that a buccal adhesive testosterone patch may affect oral health. One is that both testosterone and estrogen have been shown to have a role in the development of gingivitis. Secondly, the oral mucosa is an area of the body that is susceptible to both acute and chronic inflammation, which the physical presence of a patch may exacerbate.

Endogenous testosterone in men, as well as estradiol in women, has been shown to modulate gingival inflammation. The relationship between sex hormones and gingivitis is sufficiently recognized that puberty-associated gingivitis, menstrual cycle-associated gingivitis and pregnancy-associated gingivitis are identified as unique forms of gingivitis in the American Academy of Periodontology's classification system. The exact mechanism of action of endogenous hormones on gingivitis is not known, but recent literature suggests both a change in oral flora and a change in inflammatory response. One study in teenage boys and girls showed a positive correlation with the levels of those androgens and the proportions of gingivitis causing bacteria. Another study showed that both sex hormones modulated gingival inflammation by affecting the levels of prostaglandin E2.

In terms of the sensitivity of the oral tissues to topical assault, there is also valid cause for concern. Bacterial plaque is capable of causing an inflammatory response to the gingiva that can produce irreversible inflammatory disease that is serious enough to cause the supporting tissues of the teeth to become nonfunctional. The assault from chronic use of alcohol and /or cigarettes significantly increases the risk of developing oral cancer. Striant will be used chronically, with a new patch being placed in the mouth every 12 hours, immediately replacing the spent one. This will result in an almost constant contact between the adhesive patch (approximately the size of a dime) and the soft tissues of the mouth. Although the label will direct the patient to rotate the site between the soft tissue above the right and left incisor, this may or may not be followed. Even if followed, each site will have a chronic pattern of 12-hour exposure every day.

Interpretation of Adverse Events Monitoring

The results of the AE monitoring were very difficult to interpret. In particular, the baselining gingivitis reporting at baseline varied greatly between studies with the scores in some studies being extraordinarily low, and the decrease in the presence of gingivitis after some of the trials being both unexpected and unexplained. The aggregate results of all studies except the long-term studies COL 1621-08 and COL 1621-09 showed baseline incidence of mild and moderate gingivitis at approximately 33%, which is within the range of findings from the National Institute of Dental and Craniofacial Research (NIDCR). According to NIDCR's *National Survey of Oral Health in U.S. Employed*

Adults and Seniors: 1985-1986, estimates of 39 – 47% are the typical prevalence of mild gingivitis in the US adult population. On the other hand, COL 1621-08 and COL 1621-09, the two long-term safety studies reported baseline gingivitis prevalence as 0% and 10% respectively, which are much lower than expected. In pivotal Study COL 1621-05, the incidence of gingivitis actually decreased substantially during the treatment with Striant, increasing during the follow up exam, but still remaining lower than baseline. In the long-term studies, COL 1621-08 reported no oral pathology at baseline or 12 months, whereas COL 1621-09 showed a decrease in oral pathology from 10% to 5%. These are rather unusual findings, which bring into question the validity of these results.

In order to assess the validity of these results, it is worthwhile to look at the extent of the oral exams, how often they were measured, and who administered them. In the protocol, the investigators performed what they identified as “gum checks” at several different time points. Neither the sponsor’s protocol nor final reports go into any detail about what constituted these periodic “gum checks.” – which could theoretically vary from trained dental care providers administering a complete oral exam (using dental light, mirror, or other visual aids) to a brief visual inspection of the oral cavity by individuals without training in oral pathology. It is also not clear if the examination was performed with the patch removed or in place. The use of cursory exams would explain the number of subjects with baseline gingivitis being reported as zero in long-term safety study COL 1621-08. It would also be expected with a cursory examination that the 12-month score be zero, which it was. Some of the earlier studies reported incidences that were more realistic. However, the agreement between the agency and the sponsor was that the long-term studies COL 1621-08 and COL 1621-09 would provide the assurance of safety from the topical exposure in the oral cavity.

With respect to AEs for site irritation, a placebo group would have been helpful to determine whether the oral AE’s that surfaced were related to the testosterone in the patch, as compared to the physical presence of the patch on the site with its adhesive and other inactive ingredients. The one study that used a placebo consisted only of a single dose given to 12 men; although no difference in AE’s was detected, the sample size and time are small to make any conclusions. Therefore, the effect of testosterone itself on the oral cavity is unanswered.

Being on a clinical trial also affects subject behavior, and it is possible that oral health improved during some of the studies because subjects were more attuned to oral health care during the time of patch application. Since none of the studies were blinded, investigator bias is also a strong possibility. In addition, other than studies COL 1621-04, COL 1621-05, and the open label extensions to 6 months (COL 1621-08 and COL 1621-09), the time frames of all other studies are very short, which does not allow for detecting an oral problem of chronic use.

Although a cursory “gum check” may have been sufficient for determining safety during a phase 1 trial of short duration, neither the phase 3 trials nor the long-term safety studies included a sensitive system of insuring safety, particularly for a chronic use product such as Striant. It appears as though the likelihood of detecting the development of mild to moderate gingivitis, periodontitis, or other chronic oral pathologies may have been inadequate.

The results presented in the studies do not give any clear signal of the relationship of the patch to oral irritation, but neither do they rule it out. It is also not possible to rule out Striant as being an aid in the reduction of gingivitis or other oral pathology. Without the use of placebo (other than a small phase 1 trial), it is unknown if the prevalence of oral pathology or its fluctuations during the trials is related to testosterone, the other inactive ingredients, or the physical presence of the patch.

Tumor initiation or promotion

There is an abundance of literature containing discussion of the role of testosterone in prostate cancer. However, there is scant literature about the role of testosterone as a promoter or initiator of any form of oral cancer and studies that have been published are inconclusive. A medline search conducted on the subject of testosterone and oral tumors yielded approximately 10 relevant documents published between 1985 and the present. Two studies involved humans, whereas the remainder were conducted in rats. The first human study was a case-control study in which the testosterone levels of 102 patients with laryngeal cancer were compared to the testosterone levels in a control group of 10 healthy men. The testosterone levels in the cancer patients showed a tendency towards higher values when compared with a control group of healthy men. There is no corroborating study in the literature publication in which this study was repeated and without that, any conclusions about the relationship between testosterone and laryngeal cancers are premature. In a second human study, which relied on histological examination, researchers considered the effects in both men and women of androgens on epithelia of the thyroid gland and the striated ducts in the parotid glands. The study suggested that estradiol exerts an influence on both papillary carcinoma of the thyroid gland and pleomorphic adenoma of the parotid gland, but testosterone had no effect on these glands.

Several animal studies examined testosterone's effects on tumor induction. Although each of these studies suggests a potential link between testosterone and some oral cancers, none of the studies is conclusive without further validation, and even so, the translation to humans is not clear. These studies are summarized as follows: 1) In one study, testosterone was used as a substrate during incubation of a squamous cell carcinoma cell line from a female rat. The cells produced DHT, a metabolite of testosterone, and the androgen receptor mRNA was significantly detected in those cells. As a result the authors concluded that DNA might stimulate a squamous cell proliferation through 5alpha-reductase from testosterone. 2) In a related study, female mice with induced salivary gland tumors were given either testosterone or vehicle. The group with the testosterone had elevated levels of epidermal growth factor, but less incidence of submandibular gland carcinoma. The investigators concluded that testosterone does not promote the development of submandibular gland carcinoma in mice. 3) In another study, male mice were given the polyoma virus, and split into 3 groups – one group was castrated, one received additional testosterone, and a third was a control group. 69% of the control group developed salivary gland tumors, 90% of the testosterone-treated group developed salivary gland tumors, and 50% of the castrated group developed tumors. 4) After conducting a study of the role of testosterone in the nasal cavity tumors in rats, the authors of that study concluded that the initiation but not promotional stage of nasal and paranasal cavity tumor carcinogenesis is governed by

testosterone. By varying the time of castration for rats and the timing of testosterone injections, rats exposed to a carcinogen for nasal carcinoma developed cancer at differing rates and incidences.

These human and animal studies suggest that testosterone may be a factor in developing certain oral cancers. However, they only examine the effects of systemic testosterone, not topical. Because the intent of testosterone replacement therapy is to restore normal physiologic levels of testosterone in testosterone-deficient men, men who are supplemented are at no higher systemic risk for any of these possible cancers than the normal male population. It is well known that endogenous testosterone is linked to prostate cancer, but that has not precluded its prior approval in other dosage forms. With respect to topical application of testosterone and tumor initiation or promotion, none of the trials conducted was designed to answer that question.

Other Comments:

In the Dosage and Administration section of the sponsor's proposed labeling, there is no mention of alternating the placement of the Striant bioadhesive between the right and left sides of the mouth.

Conclusion:

Although the AE profile does not provide a strong signal that Striant contributes to oral irritation, neither can it be ruled out. The potential for Striant used chronically to contribute towards promotion or initiation of oral cancer cannot be determined from this study. It is possible that a phase 4 study, designed with a more sensitive measuring system for oral AE's and in a long-term well-monitored group could answer the question more satisfactorily than what was presented in the NDA submission.

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