Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Striant SR 30 mg Mucoadhesive Buccal Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg testosterone.

For excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Muco-adhesive, buccal tablet.
White to off-white, slim, monoconvex circular tablets. The Columbia company logo is debossed on the flat side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Striant SR is indicated for testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests *(see section 4.4, Special warnings and precautions for use).*

4.2 Posology and method of administration

Adults and the elderly: The recommended dose is one buccal tablet applied to the gum region twice daily, morning and evening, about 12 hours apart. Serum total testosterone levels and clinical symptoms should be checked during initiation of treatment, after steady state has been reached (day 2 onwards) and once the patient has become familiar with buccal application. It is recommended that serum testosterone concentrations are measured in the morning (just prior to the morning dose). Careful monitoring of serum total testosterone levels and clinical symptoms is required during maintenance treatment. It is advisable to measure serum total testosterone levels regularly. If the serum total testosterone level is above the reference range, the measurement should be repeated. Striant should be permanently discontinued if the response is not satisfactory. For example, if serum total testosterone levels are repeatedly above the normal reference range (3.0 – 10.5 ng/ml [10.4 – 36.4 nmol/L]) or if symptoms of excessive androgen exposure appear during treatment with the recommended dose, or if serum testosterone levels are repeatedly below the normal reference range and the symptoms are not corrected.
Striant SR should be placed in a comfortable position just above the incisor tooth (on either side of the mouth). Upon opening the blister, the rounded side surface of the medicinal product should be placed against the gum and held firmly in place with a finger over the lip and against the medicinal product for 30 seconds to ensure adhesion. Striant SR is designed to stay in position until removed.

In case the medicinal product fails to properly adhere to the gum or should fall off during the 12 hour dosing interval, the old medicinal product should be removed and a new one applied.
If the medicinal product falls out of position four hours or less before the next dose, replace the medicinal product with a new one which can be regarded as the second dose for the 24 hour period.
Striant SR should be applied to alternate sides of the mouth with each application. It is recommended that Striant SR be applied in the morning and evening after brushing the teeth.
Striant SR should not be chewed or swallowed, as it will not be effective. To remove Striant SR, gently slide the medicinal product downwards from the gum towards the tooth to avoid scratching the gum.

Children and adolescents: Striant SR is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.
Although the effects of eating and drinking on the adhesion of Striant SR to the gums was not specifically studied, during clinical trials patients ate and drank normally and followed their normal dental care routine with no clinically important effects on testosterone levels.

4.3 Contraindications

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, nephrotic syndrome, history of primary liver tumours and established hypercalcaemia and hypercalciuria.
Striant SR should not be used in patients with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Striant SR should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.) and confirmed by 2 separate blood testosterone measurements. There is limited experience of the use of Striant SR in elderly patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologic testosterone serum levels are lower with increasing age.
Due to variability in laboratory values, all measurements of testosterone should be carried out in the same laboratory.
Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with local recommended methods (e.g. digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).
Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.
In patients suffering from severe cardiac, hepatic or renal insufficiency, or ischemic heart disease, treatment with testosterone may cause severe complications characterised by oedema, with or without congestive heart failure.

In such cases, treatment must be stopped immediately. There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with renal or hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients.
Gynaecomastia is associated with male hypogonadal function but may develop and persist in patients on testosterone replacement therapy.
Athletes treated with testosterone replacement for primary or secondary male hypogonadism should be advised that Striant SR contains an active substance which may produce a positive reaction in anti-doping tests.
Haemoglobin and haematocrit levels should be checked periodically (to detect polycythaemia) in patients on long term androgen therapy. Liver function tests should also be checked periodically in patients on long term androgen therapy.
Testosterone should be used with caution in patients with hypertension, pre-existing cardiac, renal or hepatic disease, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possibility of water retention or oedema.
In diabetic patients, the metabolic effects of androgens may decrease blood glucose and therefore, insulin requirements.
Striant SR should be used with caution in patients with xerostomia.
Striant SR should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria) due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.
Striant SR is not a treatment for male sterility.
There are published reports of increased risk of sleep apnoea in hypogonadal subjects treated with testosterone esters, especially in those with risk factors such as obesity and chronic respiratory disease.
Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: Concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation and should be administered cautiously, particularly in patients with cardiac, renal or hepatic disease.
Anticoagulants: Testosterone and other androgens can increase the anticoagulant effect when given concomitantly with anticoagulants such as warfarin. Patients receiving anticoagulants should be monitored closely especially when starting and stopping testosterone replacement therapy.

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

4.6 Pregnancy and lactation

Striant SR is intended for use by men only. Testosterone may harm the foetus and should not be given to pregnant or breast feeding women.

4.7 Effects on ability to drive and use machines

Striant™ SR has no influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies, 311 patients were treated with Striant SR for up to 12 months. The most common adverse reaction was application site irritation which was reported by 7.7 % of patients. Other common adverse reactions (reported by 1-10% of patients) which were possibly, probably or definitely related to the use of Striant SR are listed below:

Application site irritation Headache Application site pain Fatigue Taste perversion Polycythaemia/Haematocrit increased Gingivitis Prostatic specific antigen increased Taste bitter Application site oedema Taste peculiar	All these adverse reactions were common (>1/100, <1/10)

According to the literature, other known undesirable effects have been reported following testosterone treatment and are listed in the following table:

Body System	Adverse reactions
Blood and the lymphatic system disorders	Rare cases of polycythaemia (erythrocytosis)
Metabolism and nutrition disorders	Weight gain, electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment
Musculoskeletal system	Muscle cramps
Nervous system	Nervousness, hostility, depression
Respiratory system	Sleep apnoea
Hepatobiliary disorders	In very rare cases jaundice and liver function test abnormalities
Skin and appendages	Various skin reactions may occur including acne, seborrhoea and balding (alopecia)
Reproductive system and breast disorders	Libido changes, increased frequency of erections; therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism), prostate abnormalities, prostate cancer*, urinary obstruction
General disorders and administration site conditions	High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur

* Data on prostate cancer risk in association with testosterone therapy are inconclusive.
Other rare known undesirable effects associated with excessive dosages of testosterone treatments include hepatic neoplasms.

4.9 Overdose

This is not likely due to the mode of administration. After removal of the tablets serum testosterone concentration falls to pre-treatment levels within 2-4 hours.
Oral ingestion of Striant SR will not result in clinically significant serum testosterone concentrations due to extensive first-pass (hepatic) metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, 3-oxoandrosten (4) derivatives, ATC code: G03B A03
Endogenous androgens, including testosterone and dihydrotestosterone (DHT) are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, and alterations in body musculature and fat distribution.
Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.
During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinising hormone (LH).

5.2 Pharmacokinetic properties

Absorption
Striant SR allows the slow release and absorption of testosterone through gum and cheek surfaces that are in contact with the tablet. Since venous drainage from the mouth is to the superior vena cava, trans-buccal delivery testosterone circumvents first-pass (hepatic) metabolism, thus avoiding substantial metabolism and elimination. As a result, Striant SR is able to produce circulating testosterone concentrations in hypogonadal males that approximate physiologic levels seen in healthy young men of 3.0-10.5 ng/ml (10.4-36.4 nmol/L).
Following the initial application of Striant SR, the serum testosterone concentration rises to a maximum within 10-12 hours.
Typical serum testosterone concentrations over 24 hours in clinical studies were about: average 5.40 ±1.70 ng/ml (18.72 ± 5.90 nmol/L); maximum 9.00 ±3.10 ng/ml (31.20 ± 10.75 nmol/L); minimum 3.10 ±1.40 ng/ml (10.75 ± 4.85 nmol/L).
Serum concentrations of testosterone approximate the steady-state level within 24 hours after initiation of twice daily dosing. Following tablet removal, the serum testosterone concentration decreases to a level below the normal range within 2-4 hours. Striant SR is intended for twice daily dosing, however individual tablets continue to provide physiologic levels of testosterone over application periods of up to 16 hours.

Bioavailability
An estimate of the amount of testosterone absorbed systemically from Striant SR is 3.1 (SD 1.65) mg for a 30 mg dose applied for 12 hours. Single dose application of Striant SR resulted in an average concentration of 3.9 ng/ml (13.52 nmol/L).

Distribution
Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood and increases again during the later decades of life. Approximately 40% of the testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins

Metabolism
There is a considerable variation in the half-life of testosterone as reported in the literature, ranging from 10-100 minutes. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolised to various 17-keto steroids through two different pathways, and the major active metabolites are oestradiol and dihydrotestosterone (DHT). DHT binds with greater affinity to sex hormone-binding globulin (SHBG) than does testosterone. In many tissues the activity of testosterone appears to depend on reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolised to 3-alpha and 3-beta androstanediol.
DHT concentrations increase in parallel with testosterone concentrations during Striant SR treatment. After 24 hours of treatment, mean DHT serum concentrations are within normal range. The mean steady-state T/DHT ratio during treatment with Striant SR remained close to the physiological ratio of 10.

Elimination
About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulphuric acid conjugates of testosterone and its metabolites, about 6% of a dose is excreted in the faeces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

5.3 Preclinical safety data

Testosterone has been found to be non-mutagenic in vitro using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. The clinical relevance of the latter observation is not known.
Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose dependent manner.
Pre clinical and clinical long term local tolerance data are limited.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Colloidal anhydrous silica
Talc
Hypromellose
Polycarbophil
Carbomers 974P
Maize starch
Lactose anhydrous
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Striant SR 30 mg tablets are packed in PVC/PE/PVDC/PE/PVC blisters sealed with aluminium foil. Each sheet of blisters contains 10 tablets. Pack sizes: 30 and 60 tablets in cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Once Striant SR tablets are removed from the mouth they should be disposed of safely with household waste in a manner that prevents accidental application or ingestion by children or pets.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ardana Bioscience Limited
38 Melville Street
Edinburgh
EH3 7HA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1228/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2005

10 DATE OF REVISION OF THE TEXT

October 2005