AUSTRALIAN PRODUCT INFORMATION

Andriol® Testocaps® (testosterone undecanoate) soft capsule

1 NAME OF THE MEDICINE

Testosterone undecanoate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40.0 mg testosterone undecanoate, which is equivalent to 25.3 mg testosterone.

For the full list of excipients, see Section 6.1 **List of Excipients**.

3 PHARMACEUTICAL FORM

Soft oval glossy, transparent orange coloured gelatin capsules, containing a clear yellow oil fill. The capsules are encoded with a white imprint marked ORG DV3.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Androgen replacement therapy for confirmed testosterone deficiency in males, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults including elderly
Andriol Testocaps must be taken orally with the morning and evening meal.

The capsules should be taken with some fluid and swallowed whole without chewing.

If an uneven number of capsules are to be taken, the greater dose should be taken in the morning.

The dosage of Andriol Testocaps should be determined by the physician according to the severity of the symptoms.

The initial dose is usually 120-160 mg/day for 2-3 weeks.

Subsequent dosage (40-120 mg/day) should be based on the clinical effect obtained in the first weeks of therapy.

Responses to dosage should be more closely monitored in those patients referred to under Section 4.4 **Special Warnings and Precautions for Use**.

In general, the dose should be adjusted according to the response of the individual patient.

Paediatric population
Safety and efficacy have not been adequately determined in children and adolescents. Pre-pubertal children treated with Andriol Testocaps should be treated with caution.

4.3 CONTRAINDICATIONS

- Like any androgen therapy testosterone undecanoate is contraindicated in male patients with known or suspected carcinoma of the prostate gland or breast.
- Patients with nephrosis or nephrotic phase of nephritis.
- Andriol Testocaps should not be used in case of known hypersensitivity to the active substance or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions
The following precautions are common to all testosterone containing preparations:

1. Patients with myocardial or renal dysfunction, hypertension, migraine, diabetes mellitus or epilepsy (or a history of these conditions) should be observed carefully, since androgen therapy may cause fluid retention.

2. Conditions which may be aggravated by the possible fluid retention or oedema caused by Andriol Testocaps.

3. Androgen use in prepubertal boys should be cautious and monitored carefully to avoid the possibility of premature epiphyseal fusion, or precocious sexual development. Skeletal maturation should be monitored regularly.

4. Patients with psychological disturbances should be cautiously treated since suicide due to treatment-aggravated depression has been reported.

5. The size and consistency of the prostate should be monitored periodically.

Andriol Testocaps contains Sunset Yellow FCF which may cause allergic reactions. Medical examination

Medical examination
Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

Physicians should consider monitoring patients receiving Andriol Testocaps before the start of treatment, at quarterly intervals for the first 12 months and yearly thereafter for the following parameters:

- Digital rectal examination (DRE) of the prostate and PSA to exclude benign prostate hyperplasia or a sub-clinical prostate cancer (see Section 4.3 **Contraindications**).

- Haematocrit and haemoglobin to exclude polycythaemia

Conditions that need supervision
Patients, especially the elderly, with the following conditions should be monitored for:

- **Tumours –** Mammary carcinoma, hypernephroma, bronchial carcinoma and skeletal metastases. In these patients hypercalcaemia may develop spontaneously, also during androgen therapy. The latter can be indicative of a positive tumour response to the hormonal treatment. Nevertheless, the hypercalcaemia should first be treated

appropriately and after restoration of normal calcium levels, hormone therapy can be resumed.

- **Pre-existing conditions –** In patients with pre-existing cardiac, renal or hepatic insufficiency/disease androgen treatment may cause complications characterised by oedema with or without congestive heart failure. In such cases treatment must be stopped immediately.
  Patients who experienced myocardial infarction, cardiac-, hepatic- or renal insufficiency, hypertension, epilepsy, or migraine should be monitored due to the risk of deterioration of or reoccurrence of disease. In such cases treatment must be stopped immediately.
- **Diabetes mellitus –** Androgens in general and Andriol Testocaps can improve the glucose tolerance in diabetic patients (see Section 4.5 **Interactions with other Medicines and other Forms of Interactions**).
- **Anti-coagulant therapy –** Androgens in general and Andriol Testocaps can enhance the anti-coagulant action of coumarin-type agents (see Section 4.5 **Interactions with other Medicines and other Forms of Interactions**).
- **Sleep Apnoea –**There is insufficient evidence for a recommendation regarding the safety of treatment with testosterone esters in men with sleep apnoea. Good clinical judgment and caution should be employed in patients with risk factors such as adiposity or chronic lung diseases.

Adverse events
If androgen-associated adverse reactions occur, treatment with Andriol Testocaps should be discontinued and, upon resolution of complaints, resumed with a lower dose.

(Mis)use in sports
Patients who participate in competitions governed by the World Anti-Doping Agency (WADA) should consult the WADA-code before using this product as Andriol Testocaps can interfere with anti-doping testing. The misuse of androgens to enhance ability in sports carries serious health risks and is to be discouraged.

Drug abuse and dependence
Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Abuse of testosterone and other anabolic androgenic steroids can lead to serious adverse reactions including: cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events. Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use.

The abuse of testosterone and other anabolic androgenic steroids carries serious health risks and is to be discouraged (see Section 4.8 **Adverse Effects (Undesirable Effects)**).

Use in hepatic impairment

For use in hepatic impairment see Section 4.4 **Special Warnings and Precautions for Use – Pre-existing conditions.**

Use in renal impairment

For use in renal impairment see Section 4.4 **Special Warnings and Precautions for Use – Pre-existing conditions.**

Use in the elderly

There is limited experience on the safety and efficacy of the use of Andriol Testocaps in 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 physiologically testosterone serum levels are lower with increasing age.

Paediatric use

In pre-pubertal children statural growth and sexual development should be monitored since androgens in general and Andriol Testocaps in high dosages may accelerate epiphyseal closure and sexual maturation.

Effects on laboratory tests

Androgens may decrease levels of thyroxine-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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Enzyme inducing agents such as barbiturates, may exert decreasing effects on testosterone levels.

Enzyme-inhibiting drugs may increase testosterone levels. Therefore adjustment of the dose of Andriol may be necessary. Andriol may potentiate the effects of ciclosporin and increase the risk of nephrotoxicity.

Androgens may improve glucose tolerance and thereby in diabetic patients decrease the need for insulin or other antidiabetic drugs (see Section 4.4 **Special Warnings and Precautions for Use**). Patients with diabetes mellitus should therefore be monitored especially at the beginning or end of treatment and at periodic intervals during Andriol Testocaps treatment.

High doses of androgens may enhance the anti-coagulant action of coumarin-type agents. Therefore close monitoring of prothrombin time, and if necessary a dose reduction of the anticoagulant is required during therapy.

The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation; thus these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema (see Section 4.4 **Special Warnings and Precautions for Use**).

Andriol may interfere with a number of clinical laboratory tests e.g. those for glucose tolerance and thyroid function, suppression of clotting factors II, V, VII and X.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In men treatment with androgens can lead to fertility disorders by repressing sperm-formation.

Use in pregnancy (Category D)

This drug is not intended for use in female patients and is contraindicated in pregnancy. Androgenic substances may have a virilising effect on the female foetus and should be avoided during pregnancy.

Use in lactation

This drug is not intended for use in female patients.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess the direct effect of Andriol on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Andriol is generally well tolerated. Very few side effects have been associated with the clinical use of testosterone undecanoate.

Gastrointestinal complaints Common (1 to 10%)*:* oily stools. However, these side effects were attributed to the oily solvent and were not considered serious; *Uncommon: (0.1 to 1%)* nausea.

Genitourinary Disorders Rare (< 0.1%): priapism, epididymitis, bladder irritability, gynaecomastia, impotence, inhibition of testicular function and testicular atrophy. It is possible that prolonged administration of testosterone undecanoate may induce oligospermia, or decreased ejaculatory volume, which are reversible upon cessation of the drug.

Blood Disorders Rare (< 0.1%): leukocytosis, polycythaemia and Serum cholesterol concentration may increase during androgen therapy. It is possible that prolonged administration of testosterone undecanoate may induce sodium and water retention.

Neurological Disorders Rare (< 0.1%): generalised paraesthesia, insomnia, excitation, headache, anxiety, mental depression (see Section 4.4 Special Warnings and Precautions for Use).

Hypersensitivity and Skin Disorders Uncommon *(0.1 to 1.0%):* chills, maculopapular rash, acne, flushing of skin

Others *Frequency unknown:*

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Prostatic cancer (progression of a sub-clinical prostatic cancer)

Psychiatric disorders: Nervousness, Mood altered, Libido increased, Libido decreased

Vascular disorders: Hypertension

Hepatobiliary disorders: Hepatic function abnormal

Skin and subcutaneous tissue disorders: Pruritus

Musculoskeletal and connective tissue disorders: Myalgia

Reproductive system and breast disorders: Benign prostatic hyperplasia (prostatic growth to normogonadal size)

Investigations: Lipids abnormal (decrease in serum LDL-C, HDL-C and triglycerides), PSA increased, Haematocrit increased, Red blood cell count increased, Haemoglobin increased

The terms used to describe the undesirable effects above are also meant to include synonyms and related terms.

These symptoms are remedied by a pause in treatment after which therapy should be resumed at a lower dosage.

In a few patients diarrhoea and abdominal pain/discomfort have been reported during use of Andriol Testocaps.

Drug abuse and dependence:
Testosterone, often in combination with other anabolic androgenic steroids (AAS) has been subject to abuse at doses higher than recommended for the approved indication (Section 4.4 **Special Precautions and Warnings for Use**). The following additional adverse reactions have been reported in the context of testosterone/AAS abuse:

Endocrine disorders: Secondary hypogonadism[1]

Psychiatric disorders: Hostility, Aggression, Psychotic disorder, Mania, Paranoia and Delusion

Cardiovascular disorders: Myocardial infarction, Cardiac failure, Cardiac failure chronic[1,2], Cardiac arrest, Sudden cardiac death[1], Cardiac hypertrophy[1,2], Cardiomyopathy[1], Ventricular arrhythmia, Ventricular tachycardia, Venous/arterial thrombotic and embolic events (including Deep Venous Thrombosis, Pulmonary Embolism, Coronary artery thrombosis, Carotid artery occlusion[1,2], Intracranial venous sinus thrombosis[1,2]), Cerebrovascular accident, Ischaemic stroke

Hepatobiliary disorders: Peliosis hepatis, Cholestasis[1], Liver injury, Jaundice, Hepatic failure

Skin and subcutaneous tissue disorders: Alopecia

Reproductive system and breast disorders: Testicular atrophy, Azoospermia Infertility (in males), Enlarged clitoris and Breast atrophy (in females)

[1] Has been reported with Andriol
[2] With fatal outcomes in some cases

Paediatric population:
The following undesirable effects have been reported in pre-pubertal children using androgens (Section 4.4 **Special Warnings and Precautions for Use**): precocious sexual development, an increased frequency of erections, phallic enlargement and premature epiphyseal closure.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral toxicity of testosterone undecanoate is very low. High dosages of Andriol Testocaps may cause gastrointestinal complaints due to the oily solvent contained in the capsule. Treatment may consist of emptying the stomach and supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Androgens. ATC code G03B A03

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Testosterone undecanoate (TU) is able to by-pass the liver via the lymphatic system and is therefore orally bioavailable. TU is intended as a replacement therapy for those who have abnormally low levels of natural testosterone. TU may induce a fall in LH and FSH levels to just above normal in hypergonadotrophic hypogonadal patients and may decrease hyper-reactivity to gonadorelin stimulation. However, there are also reports where there have been no changes or changes in the opposite direction. It does not change the LH and FSH plasma levels in normal patients. Restoration of testosterone levels towards normal is associated with a significant improvement in feelings of wellbeing.

TU has been shown to induce sexual maturation in agonadal boys.

Some increase in plasma oestriol is observed. In patients with a sub-normal prolactin response to thyrotrophin releasing hormone (TRH), response is normalised during TU therapy. TU does not change the response of the pituitary to luteinising hormone releasing hormone (LHRH) or to TRH; nor does it cause any abnormal effects on haematological, blood biochemical or urinary parameters or on the size and consistency of the prostate gland. Normal prolactin levels are not affected by TU administration.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of Andriol Testocaps, an important part of the active substance testosterone undecanoate is co-absorbed with the lipophilic solvent from the intestine into the lymphatic system, thus circumventing the first-pass inactivation by the liver. During absorption testosterone undecanoate is partly reduced to dihydrotestosterone undecanoate.

Distribution

From the lymphatic system it is released into the plasma. In plasma and tissues both testosterone undecanoate and dihydrotestosterone undecanoate are hydrolysed to yield the natural male androgens testosterone and dihydrotestosterone.

Single administration of 80-160 mg Andriol Testocaps leads to a clinically significant increase of total plasma testosterone with peak levels of approximately 40 nmol/L (C_{max}), reached approximately 4-5 hours (t_{max}) after administration. Plasma testosterone levels remain elevated for at least 8 hours.

Because of the new Andriol Testocaps presentation a new bioequivalence study was conducted. An open-label, replicate, four period, cross-over trial was performed in 28 healthy postmenopausal women aged 45-65 years, with a body mass index between 18 and 30 kg/m^2 and testosterone levels ≤ 0.87 ng/mL. This study was designed to assess bioequivalence between TU administration in the Andriol Testocaps and Andriol formulation, by comparing the AUC and C_{max} of serum testosterone after administration of both formulations.

The geometric least-squares mean values (CV%) of the pharmacokinetic parameters for testosterone and baseline-corrected testosterone, and the results of average bioequivalence testing are summarized in **Table 1**. Based on C_{max} and AUC of testosterone and baseline

corrected testosterone, average bioequivalence between TU in Andriol Testocaps and Andriol is concluded.

Table 1: Bioequivalence testing between Andriol® Testocaps® and Andriol®

Parameter (units)	Andriol Testocaps Mean* (CV**) (n=27)	Andriol Mean* (CV**) (n=27)	Ratio AT/A	90% confidence interval	Acceptance Range	Conclusion
Bioequivalence testing based on serum testosterone						
C_{max} (ng/mL)	5.67 (27.25)	5.29 (40.50)	1.07	0.97 – 1.18	0.70 - 1.43	Bioequivalent
$AUC_{0\text{-tlast}}$ (ng•h/mL)	26.73 (25.68)	28.00 (30.23)	0.95	0.92 – 1.00	0.80 - 1.25	Bioequivalent
Bioequivalence testing based on baseline corrected serum testosterone						
C_{max} (ng/mL)	5.43 (28.25)	5.06 (41.75)	1.07	0.97 – 1.19	0.70 – 1.43	Bioequivalent
$AUC_{0\text{-tlast}}$ (ng•h/mL)	21.42 (28.72)	22.93 (32.26)	0.93	0.89 - 0.98	0.80 – 1.25	Bioequivalent

* geometric least-squares means; ** coefficients of variation derived from SD of log-transformed values; AT: Andriol Testocaps; A: Andriol; bioequivalent: 90% C.I. contained within the acceptance range.

Food Effect

An open label, single-centre, two-way cross-over, food interaction study with Andriol Testocaps was performed in 16 healthy postmenopausal women aged 45-65 years, with a body mass index between 18 and 30 kg/m^2 and testosterone levels ≤ 1.0 ng/mL. This study was designed to assess the effect of food on the bioavailability of testosterone (as measured by C_{max} and AUC) after a single administration of Andriol Testocaps.

Following administration of Andriol Testocaps in the fasted state a poor bioavailability of testosterone was observed, which was considerably increased when Andriol Testocaps was taken with food (see **Figure 1**). Food-effect testing based on C_{max} and $AUC_{0\text{-tlast}}$ of testosterone as well as baseline-corrected testosterone confirmed the presence of a food effect (see **Table 2**). This leads to the conclusion that Andriol Testocaps must be taken with a meal.

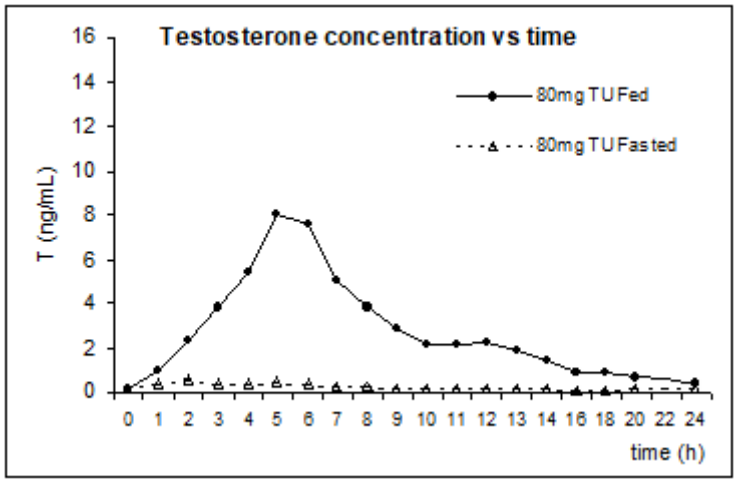


Figure 1: Mean Testosterone Concentration-Versus-Time Curve.

Table 2: Summary of food-effect testing

Compound	Parameter (unit)	Mean Fed (n=16)	Mean Fasted (n=16)	Ratio Fed/Fasted	90 % CI	Conclusion
T	C_{max} (ng/mL)	10.32	0.5095	20.26	15.47-26.54	Food-effect present
	$AUC_{0\text{-}t_{last}}$ (ng·h/mL)	53.14	4.227	12.57	9.05-17.46	Food-effect present
Baseline-corrected T	C_{max} (ng/mL)	10.15	0.2876	35.30	24.00-51.91	Food-effect present
	$AUC_{0\text{-}t_{last}}$ (ng·h/mL)	49.00	0.9402	52.11	30.94-87.76	Food-effect present

Means are geometric least-squares means; T: testosterone
Food-effect present: 90% C.I. outside acceptance range 0.80-1.25

Metabolism

Testosterone and dihydrotestosterone are metabolised via the normal pathways.

Excretion

Excretion mainly takes place via the urine as conjugates of etiocholanolone and androsterone.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

The potential carcinogenicity of testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical uterine tumours, which metastasized in some cases. There is suggestive evidence that injection of testosterone in some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to act as a tumour promoter and has been shown to increase the number of tumours and decrease the degree of differentiation of chemically induced carcinomas in the liver of rats. There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens, particularly the 17-alpha-alkyl-androgens, in high doses. Withdrawal of the drugs did not lead to regression of the tumours in all cases. Whether there is a causal relationship or a connection between testosterone administration and formation of tumours occurring by chance remains unclarified. Chronic and androgen deficiency, however, is a protective factor for prostatic disease and hypogonadal men receiving androgen replacement therapy require surveillance for prostate disease similar to that recommended for eugonadal men of comparable age. Geriatric patients treated with

androgens may be at an increased risk for the development for prostatic hyperplasia and prostatic cancer. However, there is no clear understanding of the formation and progression of prostatic carcinoma nor of the role of androgens.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents

Each capsule contains about 293 mg of a mixture of hydrogenated castor oil and propylene glycol monolaurate.

Capsule shell ingredients

The soft capsule shell contains the non active substances: gelatin, glycerol, medium chain triglycerides, lecithin, sunset yellow FCF and printed with Opacode WB water based monogramming ink NSP-78-18022 White.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Do not refrigerate.

Keep the blister in the outer carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Andriol Testocaps pack sizes are: 30s*, 60s and 120s*

The capsules are packed in PVC/Aluminium blister pack of 10, further packed into PE/AL/LDPE sachet in a carton.

*Some pack sizes may not be currently marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

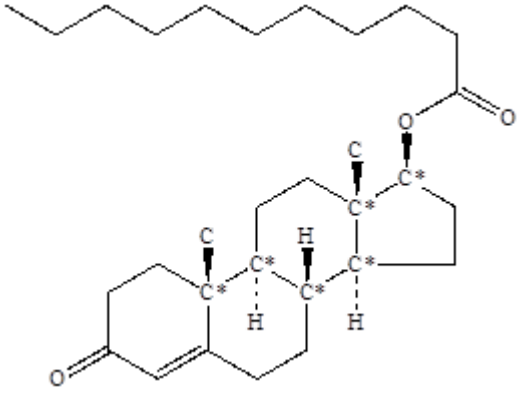
Chemical name: 3-oxo-androst-4-en-17β-yl undecanoate

Molecular Formula: $C_{30}H_{48}O_3$

Molecular Weight: 456.7

Chemical structure

The structural formula of testosterone undecanoate is:



Testosterone undecanoate, is a white to creamy-white crystalline powder. It is practically insoluble in water, soluble in 2% (w/v) dioxane and in ethanol (96%) and has a melting point of 60-65°C. It is a fatty acid ester of the naturally occurring androgen testosterone.

CAS number

5949-44-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Medicine

8 SPONSOR

Name and Address of the Sponsor in Australia
Merck Sharp & Dohme (Australia) Pty. Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

Name and Address of the Sponsor in New Zealand
Merck Sharp & Dohme (New Zealand) Ltd
P O Box 99 851
Newmarket
Auckland 1149
New Zealand

9 DATE OF FIRST APPROVAL

14 July 2003

10 DATE OF REVISION

09 October 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Convert to new format