ABPI COMPENDIUM OF DATA SHEETS

AND

SUMMARIES OF PRODUCT CHARACTERISTICS

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With The Code of Practice for the
Pharmaceutical Industry

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Special warnings and special precautions for use: Before therapy is initiated, a thorough medical history should be taken. A complete gynaecological examination should be performed and repeated at least once a year during therapy.

Prolonged use without addition of a progestogen may cause endometrial hyperplasia. Therefore, in women with an intact uterus, Sandrena treatment should be combined with cyclic progestogen administration. Withdrawal bleeding resembling normal menstruation will usually occur after each course of progestogen. The cause of unexpected or prolonged uterine bleeding during therapy should be clarified. Atypical adenomatous hyperplasia of the endometrium must be treated before commencing oestrogen therapy.

Consider discontinuation prior to surgery or prolonged immobilisation. Development of de novo frequent severe headaches or migraine should be investigated and possible prodromal symptoms of vascular occlusion should be clarified.

The risks and benefits of treatment should be evaluated and close monitoring performed for patients with:

- endometriosis
- uterine leiomyoma
- endometrial hyperplasia (simple glandular hyperplasia or hyperplasia glandularis cystica)
- diseases of the cardiovascular system including cerebrovascular disorders,
- a history of thromboembolic disease,
- severe hypertension,
- history of (or close family history of) breast cancer,
- severe disturbances of lipid metabolism,
- renal dysfunction
- systemic lupus erythematosus
- porphyria

At present there is suggestive evidence of a slight increase in the relative risk of carcinoma of the breast with long-term hormone replacement therapy, however, the results are contradictory. Regular breast examinations and mammography, where appropriate, should be carried out in women on hormone replacement therapy.

Some conditions may be aggravated during oestrogen therapy or pregnancy. Women on Sandrena treatment with one of the following conditions (or with a history thereof during previous pregnancy or hormone use) should therefore be closely monitored.

These conditions include:

- mild hypertension,
- migraine or severe headache,
- benign breast disease,
- liver function disturbances,
- cholestasis,
- cholelithiasis,
- diabetes mellitus,
- asthma,
- otosclerosis,
- multiple sclerosis,
- galactorrhea, elevated prolactin levels,
- history of herpes gestationis,
- epilepsy.

Interaction with other medicaments and other forms of interaction: No interactions between Sandrena and other medicines have been reported. There are some indications that oestrogens may reduce the effects of antihypertensive, anticoagulant and antidiabetic drugs. Concomitant treatment with potent inducers of liver enzymes (e.g. barbiturates, carbamazepine, griseofulvin and rifampicin) may reduce the plasma levels of oestradiol. The significance of these interactions in transdermal application has not been elucidated.

Pregnancy and lactation: Sandrena is not indicated in women of child-bearing capacity. It has no contraceptive efficacy. Sandrena should not be used during pregnancy or lactation.

Effects on ability to drive and use machines: Oestrogens such as Sandrena do not affect the ability to drive or use machines.

Undesirable effects: Adverse drug reactions are usually mild and only seldom lead to discontinuation of treatment. If they do occur, it will usually be during the first months of treatment.

Occasionally for oestrogens in general: Breast tenderness, headache, oedema, weight increase, unscheduled vaginal bleeding or spotting.

Rarely for oestrogens in general: Migraine, changes in libido and mood, gastrointestinal discomfort (e.g. nausea, vomiting, stomach cramps), hypertension, alterations in liver function and biliary flow.

In clinical trials dermal irritation has been very infrequent with Sandrena.

Overdosage: Generally, oestrogens are well tolerated even in massive doses. Possible symptoms of overdose include those listed under undesirable effects. Treatment is symptomatic.

Pharmacological properties Therapeutic classification: G03 CA 03, Oestrogen preparation for hormone replacement therapy.

Pharmacodynamic properties: The pharmacodynamics of Sandrena are similar to those of oral oestrogens, but the major difference to oral administration lies in the pharmacokinetic profile.

The clinical efficacy of Sandrena in the treatment of menopausal symptoms is comparable to that of peroral oestrogen. Combined with medroxyprogesterone acetate, percutaneous oestradiol lowers total cholesterol without reducing the HDL cholesterol level.

Pharmacokinetic properties: Sandrena is an alcohol-based oestradiol gel. When applied to the skin the alcohol evaporates rapidly and oestradiol is absorbed through the skin into the circulation. To some extent, however, the oestradiol is stored in the subcutaneous tissue from where it is released gradually into circulation. Percutaneous administration circumvents the hepatic first-pass metabolism. For these reasons, the fluctuations in the plasma oestrogen concentrations with Sandrena are less pronounced than peroral oestrogen.

A 1.5 mg percutaneous dose of oestradiol (1.5 g Sandrena) results in a plasma concentration of about 340 pmol/l, which corresponds to the level of early follicular stage in premenopausal women. During Sandrena treatment the oestradiol/oestrone ratio remains at 0.7, while during peroral oestrogen treatment it usually drops to less than 0.2.

The mean oestradiol exposure at steady state of Sandrena is 82 per cent compared with an equivalent oral dose of oestradiol valerate. Otherwise the metabolism and excretion of transdermal oestradiol follow the fate of natural oestrogens.

Preclinical safety data: Oestradiol is a natural female hormone with an established clinical use, therefore no toxicological studies have been performed with Sandrena. The necessary studies on the irritant effects of the gel have been studied in rabbits and skin sensitisation in guinea pig. Based on the results from these studies it can be concluded that Sandrena could very infrequently cause mild skin irritation. The frequency of the occurrence of dermal irritation can be reduced by daily change of the application site.

Pharmaceutical particulars
List of excipients: Carbomer 934 BP; Sodium hydroxide; Propylene glycol PhEur; Spir. fort.–Ethanol 96% BP, Aq. purif.–Purified water PhEur.

Incompatibilities: No incompatibilities have been found.

Shelf life: 3 years.

Special precautions for storage: At room temperature (below 25°C).

Nature and contents of container: Single dose aluminium foil sachets supplied in packages containing 28 of either dose or 91 sachets of 1 mg dose.

Instructions for use/handling: None

Marketing authorisation holder
Orion Corporation, Orioninite 1, P.O. Box 65, FIN-02101, ESPOO, FINLAND
Distributed by Organon Laboratories Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 0FL.

Marketing authorisation number 13911/0004-0005

Date of (partial) revision of the text October 1996

Legal Category POM

SUSTANON* 100

Qualitative and quantitative composition
Testosterone propionate PhEur 20 mg
Testosterone phenylpriopionate BP 40 mg
Testosterone isocaproate BP 40 mg
(Equivalent to a total of 74 mg of testosterone)

Pharmaceutical form Sustanon 100 is a clear, sterile, oily solution for deep intramuscular injection.

Clinical particulars
Therapeutic indications: Testosterone replacement therapy in male hypogonadal disorders, for example: after castration; eunuchoidism; hypopituitarism; endocrine impotence; male climacteric symptoms like decreased libido; certain types of infertility due to disorders of spermatogenesis.

Testosterone therapy may also be indicated for the prevention and treatment of osteoporosis in hypogonadal males

Posology and method of administration:
Dosage: In general, dosage should be adjusted to the individual response of the patient.

Adults: Usually, one injection of 1 ml per two weeks is adequate.

Elderly: It should be noted that smaller and less frequent doses may achieve the same response.

Children: It should be noted that smaller and less frequent doses may achieve the same response.

Administration: Deep intramuscular injection

Contra-indications: Known or suspected prostatic or mammary carcinoma. Pregnancy. Breast-feeding. Hypersensitivity to one of the excipients.

Special warnings and special precautions for use: Patients, especially the elderly, with the following conditions should be monitored: ischaemic heart disease, since androgens may produce hypercholesterolaemia; latent or overt cardiac failure, renal dysfunction, hypertension, epilepsy or migraine (or a history of these conditions), since androgens may occasionally induce fluid and sodium retention; skeletal metastases, since androgens may induce hypercalcaemia or hypercalciuria in these patients.

The use of steroids may influence the results of certain laboratory tests.

Androgens should be used cautiously in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development.

If androgen-associated adverse reactions occur, Sustanon 100 treatment should be interrupted and, after disappearance of the symptoms, be resumed at a lower dosage.

Interaction with other medicaments and other forms of interaction: Enzyme-inducing agents may exert increasing or decreasing effects on testosterone levels. Therefore adjustment of the dose, and/or intervals between injections may be required.

Pregnancy and lactation: On the basis of its pharmacological effect, Sustanon 100 is suspected to cause birth defects and/or other irreversible adverse effects on pregnancy outcome. Therefore, Sustanon 100 is contraindicated during pregnancy and lactation.

Effects on ability to drive and use of machines: As far as is known Sustanon 100 has no influence on alertness and concentration

Undesirable effects: The following adverse reactions have been associated with androgen therapy in general: In prepubertal boys, precocious sexual development, an increased frequency of erections, phallic enlargement and premature epiphyseal closure; priapism and other signs of excessive sexual stimulation; water and sodium retention; oligospermia and a decreased ejaculatory volume.

Treatment should be interrupted until these symptoms have disappeared, after which it should be continued at a lower dosage.

Hoarseness of the voice may be the first symptom of vocal change which may lead to irreversible lowering of the voice. If signs of virilisation, particularly lowering of the voice, develop, treatment should be discontinued.

Overdosage: The acute intramuscular toxicity of Sustanon 100 is very low. Therefore toxic symptoms are not expected to occur.

Pharmacological properties
Pharmacodynamic properties: Testosterone is the principal endogenous hormone essential for normal growth and development of the male sex organs and male secondary sex characteristics. During adult life testosterone is essential for the functioning of the testes and accessory structures, and for the maintenance of libido, sense of well-being, erectile potency, prostate and seminal vesicle function.

Treatment of hypogonadal males with Sustanon 100 results in a clinically significant rise of plasma concentrations of testosterone, dihydrotestosterone and androstenedione, as well as a decrease of SHBG (sex hormone binding globulin). In the males with primary (hypergonadotropic) hypogonadism treatment with Sustanon results in a normalisation of pituitary function.

Pharmacokinetic properties: Sustanon 100 contains a number of esters of testosterone with different durations of action. The esters are hydrolysed into the natural hormone testosterone, as soon as they enter the general circulation.

A single dose of Sustanon 100 leads to an increase of total plasma testosterone, with peak level reached approximately 24-48hrs (t_{max}) after administration. Plasma testosterone levels return to the lower limit of the normal range in males after approximately 21 days.

Testosterone is metabolised via the normal pathways. Excretion mainly takes place via the urine as conjugates of etiocholanolone and androsterone.

Preclinical safety data: Not applicable.

Pharmaceutical particulars
List of excipients:
Benzyl Alcohol PhEur 0.1 ml
Arachis Oil PhEur to 1.0 ml

Incompatibilities: No relevant incompatibilities are known.

Shelf-life: 5 years.

Special precautions for storage: Store between 15-25°C, protect from light.

Nature and contents of containers: 1 ml ampoules in boxes of 3.

Instructions for use/handling: not applicable.

Marketing authorisation number 0065/5019

Date of first authorisation 28 February 1973

Date of preparation of the text March 1995

Legal category POM

SUSTANON* 250

Qualitative and quantitative composition
Testosterone propionate PhEur 30 mg
Testosterone phenylpriopionate BP 60 mg
Testosterone isocaproate BP 60 mg
Testosterone decanoate BP 100 mg
(equivalent to a total of 176 mg of Testosterone)

Pharmaceutical form Sustanon 250 is a clear, sterile, oily solution for deep intramuscular injection.

Clinical particulars
Therapeutic indications: Testosterone replacement therapy in male hypogonadal disorders, for example: after castration; eunuchoidism; hypopituitarism; endocrine impotence; male climacteric symptoms like decreased libido; certain types of infertility due to disorders of spermatogenesis.

Testosterone therapy may also be indicated for the prevention and treatment of osteoporosis in hypogonadal males

Posology and method of administration:
Dosage: In general, dosage should be adjusted to the individual response of the patient.

Adults: Usually, one injection of 1 ml per three weeks is adequate.

Elderly: It should be noted that smaller and less frequent doses may achieve the same response.

Children: It should be noted that smaller and less frequent doses may achieve the same response.

Administration: Deep intramuscular injection

Contra-indications: Known or suspected prostatic or mammary carcinoma. Pregnancy. Breast-feeding. Hypersensitivity to one of the excipients.

Special warnings and special precautions for use: Patients, especially the elderly, with the following conditions should be monitored: ischaemic heart disease, since androgens may produce hypercholesterolaemia. Latent or overt cardiac failure, renal dysfunction, hypertension, epilepsy or migraine (or a history of these conditions), since androgens may occasionally induce fluid and sodium retention. Skeletal metastases, since androgens may induce hypercalcaemia or hypercalciuria in these patients.

The use of steroids may influence the results of certain laboratory tests.

Androgens should be used cautiously in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development.

If androgen-associated adverse reactions occur, Sustanon 250 treatment should be interrupted and, after disappearance of the symptoms, be resumed at a lower dosage.

Interaction with other medicaments and other forms of interaction: Enzyme-inducing agents may exert increasing or decreasing effects on testosterone levels. Therefore adjustment of the dose, and/or intervals between injections may be required.

Pregnancy and lactation: On the basis of its pharmacological effect, Sustanon 250 is suspected to cause birth defects and/or other irreversible adverse effects on pregnancy outcome. Therefore, Sustanon 250 is contraindicated during pregnancy and lactation.

Effects on ability to drive and use of machines: As far as is known Sustanon 250 has no influence on alertness and concentration.

Undesirable effects: The following adverse reactions have been associated with androgen therapy in general:

In prebubertal boys, precocious sexual development, an increased frequency of erections, phallic enlargement and premature epiphyseal closure; priapism and other signs of excessive sexual stimulation; water and sodium retention; oligospermia and a decreased ejaculatory volume.

Treatment should be interrupted until these symptoms have disappeared, after which it should be continued at a lower dosage.

Hoarseness of the voice may be the first symptom of vocal change which may lead to irreversible lowering of the voice. If signs of virilisation, particularly lowering of the voice, develop, treatment should be discontinued.

Overdosage: The acute intramuscular toxicity of Sustanon 250 is very low. Therefore toxic symptoms are not expected to occur.

Pharmacological properties
Pharmacodynamic properties: Testosterone is the principal endogenous hormone essential for normal growth and development of the male sex organs and male secondary sex characteristics. During adult life testosterone is essential for the functioning of the testes and accessory structures, and for the maintenance of libido, sense of well-being, erectile potency, prostate and seminal vesicle function.

Treatment of hypogonadal males with Sustanon 250 results in a clinically significant rise of plasma concentrations of testosterone, dihydrotestosterone and androstenedione, as well as a decrease of SHBG (sex hormone binding globulin). In the males with primary (hypergonadotropic) hypogonadism treatment with Sustanon results in a normalisation of pituitary function.

Pharmacokinetic properties: Sustanon 250 contains a number of esters of testosterone with different durations of action. The esters are hydrolysed into the natural hormone testosterone as soon as they enter the general circulation.

A single dose of Sustanon 250 leads to an increase of total plasma testosterone with peak-levels of approximately 70 nmol\l (C_{max}), which are reached approximately 24-48h (t_{max}) after administration. Plasma testosterone levels return to the lower limit of the normal range in males in approximately 21 days.

Testosterone is metabolised via the normal pathways. Excretion mainly takes place via the urine as conjugates of etiocholanolone and androsterone.

Preclinical safety data: Not applicable.

Pharmaceutical particulars
List of excipients:
Benzyl Alcohol PhEur 0.1 ml
Arachis Oil PhEur to 1.0 ml

Incompatibilities: No relevant incompatibilities are known.

Shelf-life: 5 years

Special precautions for storage: Store between 15-25°C, protect from light

Nature and contents of containers: 1 ml ampoules in boxes of 3

Instructions for use/handling: not applicable.

Marketing authorisation number 0065/5086

Date of first authorisation 28 February 1973

Date of preparation of the text March 1995

Legal category POM

TESTOSTERONE IMPLANT

Presentation Testosterone implants are pellets containing 50, 100 or 200 mg testosterone in glass ampoules.

Uses In the male: testosterone replacement therapy in primary or secondary hypogonadal disorders, for example:

- after castration,
- eunuchoidism,
- hypopituitarism,
- endocrine impotence,
- infertility due to spermatogenic disorders,
- male climacteric symptoms such as decreased libido and decreased mental and physical activity.

Moreover, testosterone therapy may be indicated in osteoporosis in the male due to androgen deficiency.

In the female as an adjunct to oestrogen replacement therapy in postmenopausal women to alleviate symptoms, such as decreased libido and/or loss of energy.

Dosage and administration
In males: 100-600 mg depending on individual requirements. A dosage of 600 mg (6 x 100 mg) usually maintains plasma testosterone levels within the normal physiological range for 4-5 months.

In females: 50-100 mg as an adjunct to oestradiol implants.

Method of implantation: Testosterone implants should be inserted subcutaneously into an area where there is relatively little movement or blood supply, such as the lower abdominal wall or the buttock. Insertion is made under local anaesthesia using a trocar and a cannula. The wound is closed either with an adhesive dressing or a fine suture. The implants must be placed subcutaneously to facilitate removal if necessary. Full aseptic 'no touch' technique should be adopted.

Contra-indications, warnings, etc.
Contra-indications: Known or suspected prostatic carcinoma or breast carcinoma in the male. Pregnancy. Breast-feeding.

Use in pregnancy and lactation: Testosterone implants are contra-indicated during pregnancy and lactation.

Warnings and precautions:

- Androgens should be used with caution in women to avoid unacceptable and irreversible virilization. Female patients should therefore be counselled to report any deepening or hoarsening of the voice without delay.
- Androgens should be used with caution in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development. Skeletal maturation should be monitored regularly.
- Due to the long-lasting action and the difficulty of removal, Testosterone implants should be used with extra caution. Therefore, it may be advisable to establish the beneficial effect and tolerance for androgen therapy by prior treatment with a shorter-acting testosterone preparation. This applies in particular to (pre)pubertal boys, women and elderly men.
- Patients with latent or overt cardiac failure, renal or hepatic dysfunction, hypertension, epilepsy or migraine (or a history of these conditions) should be kept under close medical supervision, since aggravation of recurrence may occasionally be induced.
- If androgen-associated adverse reactions occur the implant should be removed if possible.
- The use of steroids may influence the results of certain laboratory tests.

Effects on ability to drive and to use machines: As far as is known Testosterone implants have no effects on alertness and concentration.

Interactions: Enzyme-inducing drugs may influence plasma testosterone levels.

Other undesirable effects (frequency and seriousness): The following adverse reactions have been associated with androgen therapy:

- *in general:* water and sodium retention, hypercalcaemia;
- *in women:* symptoms of virilization, such as voice changes (deepening, hoarsening) and hirsutism;
- *in prepubertal boys:* precocious sexual development, increased frequency of erections, phallic enlargement and premature epiphyseal closure;
- *in men:* priapism and other signs of excessive sexual stimulation, oligospermia and decreased ejaculatory volume

Overdosage: The acute toxicity of testosterone is low. Priapism in men and undesired deepening of the voice in women are symptoms of chronic overdosage. In this case the implant(s) should be removed.

Pharmaceutical precautions Store below 25°C and protect from light

Incompatibilities: None.

Legal category POM.

Package quantities Each sterile implant is supplied singly, in a sealed glass tube.

Further information Testosterone is a naturally-occurring hormone formed in the interstitial cells of the testes under the control of the anterior lobe of the pituitary gland which controls the development and maintenance of the male sex organs and male secondary sex characteristics. Testosterone also produces systemic effects, such as increasing the retention of nitrogen, calcium, sodium, potassium, chloride and phosphate leading to an increase in skeletal weight, water retention and an increase in the growth of bone.

Testosterone implants, when inserted subcutaneously release testosterone into the bloodstream at a relatively even rate supplying near physiological plasma testosterone levels.

Surface area of the implants is the most important factor influencing the rate of absorption. In general the absorption rate estimated by removal of implants at intervals and weighing appears to be appreciably more rapid than when the rate is assessed upon the clinical requirement. In addition to clinical evidence individual variation in the rate of absorption of implants must be taken into account.

The average daily absorption of testosterone has been estimated at 0.5 mg for a 100 mg implant with an approximate duration of 30 weeks.

Product licence numbers

50 mg	0065/5082R
100 mg	0065/5083R
200 mg	0065/5084R

ZISPIN ▼

Qualitative and quantitative composition Each tablet contains 30 mg of mirtazapine.

Pharmaceutical form Tablet