ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Livensa 300 micrograms/24 hours transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch of 28 cm^2 contains 8.4 mg testosterone and provides 300 micrograms of testosterone per 24 hours.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, clear, oval matrix-type transdermal patch consisting of three layers: a translucent backing film, an adhesive matrix drug layer, and a protective release liner that is removed prior to application. Each patch surface is stamped with T001.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Livensa is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant estrogen therapy.

4.2 Posology and method of administration

Posology

The recommended daily dose of testosterone is 300 micrograms. This is achieved by applying the patch twice weekly on a continuous basis. The patch should be replaced with a fresh patch every 3 to 4 days. Only one patch is to be worn at a time.
Livens
Concomitant estrogen treatment
The appropriate use and restrictions associated with estrogen therapy should be considered before Livensa therapy is initiated and during routine re-evaluation of treatment. Continued use of Livensa is only recommended while concomitant use of estrogen is considered appropriate (i.e. the lowest effective dose for the shortest possible duration).

Patients treated with conjugated equine estrogen (CEE) are not recommended to use Livensa, as efficacy has not been demonstrated (see sections 4.4 and 5.1).

Duration of treatment
Livensa treatment response should be evaluated within 3-6 months of initiation, to determine if continued therapy is appropriate. Patients who do not experience a meaningful benefit should be re-evaluated and discontinuation of therapy be considered.

As the efficacy and safety of Livensa have not been evaluated in studies of longer duration than 1 year, it is recommended that an appraisal of the treatment is undertaken every 6 months.

Special populations

Renal impairment
No studies have been conducted in patients with renal insufficiency.

Hepatic impairment
No studies have been conducted in patients with hepatic impairment.

Elderly
Livensa is recommended for use in surgically menopausal women up to the age of 60. Consistent with the prevalence of HSDD, there are limited data above the age of 60.

Paediatric population
There is no relevant use of Livensa in the paediatric population.

Method of administration

The adhesive side of the patch should be applied to a clean, dry area of skin on the lower abdomen below the waist. A particular application site should be rotated with an interval of at least 7 days between applications. Patches should not be applied to the breasts or other body regions. A skin site with minimal wrinkling and not covered by tight clothing is recommended. The site should not be oily, damaged, or irritated. To prevent interference with the adhesive properties of Livensa, no creams, lotions or powder should be applied to the skin where the patch is to be applied.

The patch should be applied immediately after opening the sachet and removing both parts of the protective release liner. The patch should be pressed firmly in place for about 10 seconds, making sure there is good contact with the skin, especially around the edges. If an area of the patch lifts, pressure should be applied to that area. If the patch detaches prematurely, it may be reapplied. If the same patch cannot be reapplied, a new patch should be applied to another location. In either case, the original treatment regimen should be maintained. The patch is designed to remain in place during a shower, bath, swimming or exercising.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Known, suspected or past history of cancer of the breast or known or suspected estrogen-dependent neoplasia, or any other condition consistent with the contraindications for the use of estrogen.

4.4 Special warnings and precautions for use

Special warnings

Androgenic reactions
At regular intervals during treatment, physicians should monitor patients for potential androgenic undesirable reactions (e.g. acne, changes in hair growth or hair loss). Patients should be advised to self assess for androgenic undesirable effects. Signs of virilisation, such as voice deepening, hirsutism or clitoromegaly, may be irreversible and discontinuation of treatment should be considered. In clinical trials these reactions were reversible in the majority of patients (see section 4.8).

Hypersensitivity
Severe skin erythema, local oedema and blistering may occur due to hypersensitivity to the patch at the site of application. Use of the patch should be discontinued if this occurs.

Long-term safety, including breast cancer
The safety of Livensa has not been evaluated in double blind placebo controlled studies of longer than 1 year duration. There is little information on long-term safety, including effects on breast tissue, the cardiovascular system and increase in insulin resistance.

Data in the literature regarding the influence of testosterone on the risk of breast cancer in women are limited, inconclusive and conflicting. The long-term effect of testosterone treatment on the breast is currently unknown, therefore patients should be carefully monitored with regard to breast cancer in accordance with currently accepted screening practises and individual patient needs.

Cardiovascular disease
Patients with known cardiovascular disease have not been studied. Patients with cardiovascular risk factors, in particular hypertension, and patients with known cardiovascular disease should be carefully monitored, specifically regarding changes in blood pressure and weight.

Diabetic patients
In diabetic patients the metabolic effects of testosterone may decrease blood glucose and therefore insulin requirements. Patients with diabetes mellitus have not been studied.

Endometrial effects
Little information is available on the effects of testosterone on the endometrium. The limited data evaluating the effect of testosterone on the endometrium neither allow conclusions nor reassurances on the incidence of endometrial cancer.

Oedema
Oedema (with or without congestive heart failure) may be a serious complication from high doses of testosterone or other anabolic steroids in patients with pre-existing cardiac, renal, or hepatic disease. However, this is not expected from the low dose of testosterone delivered by the Livensa patch.

Precautions for use

Livensa should not be used in naturally menopausal women
Efficacy and safety of Livensa in naturally menopausal women with HSDD on concomitant estrogen, with or without progestogen, have not been evaluated. Livensa is not recommended in naturally menopausal women.

Livensa should not be used in women on concomitant CEE
Whereas Livensa is indicated with concomitant estrogen therapy, the subgroup of patients receiving oral conjugated equine estrogens (CEE) did not demonstrate a significant improvement in sexual function. Therefore, Livensa should not be used in women on concomitant CEE (see sections 4.2 and 5.1).

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. When testosterone is given concomitantly with anticoagulants, the anticoagulant effect may increase. Patients receiving oral anticoagulants require close monitoring, especially when testosterone therapy is started or stopped.

4.6 Fertility, pregnancy and lactation

Pregnancy
Livensa must not be used in women who are or may become pregnant.

Testosterone may induce virilising effects on the female foetus when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

In case of inadvertent exposure during pregnancy, use of Livensa must be discontinued.

Breastfeeding
Livensa must not be used by breast-feeding women.

Fertility
No data is available of the effect of Livensa on fertility.

4.7 Effects on ability to drive and use machines

Livensa has no influence on the ability to drive and use machines. However, patients should be informed that migraine, insomnia, disturbance in attention and diplopia have been reported during treatment with Livensa.

4.8 Undesirable effects

Summary of the safety profile
The adverse reaction most often reported (30.4 %) was application site reactions. The majority of these adverse reactions consisted of mild erythema and itching and did not result in patient withdrawal.

Hirsutism was also very commonly reported. Most reports concerned the chin and upper lip, were mild (≥ 90 %), and less than 1 % of all patients withdrew from the studies due to hirsutism. Hirsutism was reversible in the majority of patients.

Other androgenic reactions commonly reported were acne, voice deepening and alopecia. More than 90 % of these reports were considered mild. These reactions were reversible in the majority of patients. Less than 1 % of patients withdrew from the studies because of any of these reactions. All other common adverse reactions resolved in the majority of patients.

Tabulated list of adverse reactions
During 6-month double blind exposure the following adverse reactions occurred in the treatment group (n=549) at a greater incidence than placebo (n=545) and were assessed by the investigators as possibly or probably related to Livensa treatment. If an adverse reaction occurred at a higher frequency in the integrated phase III studies (Livensa patients n=1,498, placebo patients n=1,297), this frequency is reported in the table. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System organ class	Very common	Common	Uncommon
Infections and infestations			Sinusitis
Blood and lymphatic system disorders			Abnormal clotting factor
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders			Increased appetite
Psychiatric disorders		Insomnia	Agitation, anxiety
Nervous system disorders		Migraine	Disturbance in attention, dysgeusia, impaired balance, hyperaesthesia, oral paraesthesia, transient ischemic attack
Eye disorders			Diplopia, eye redness
Cardiac disorders			Palpitations
Respiratory, thoracic and mediastinal disorders		Voice deepening	Nasal congestion, throat tightness

MedDRA System organ class	Very common	Common	Uncommon
Gastrointestinal disorders		Abdominal pain	Diarrhoea, dry mouth, nausea
Skin and subcutaneous tissue disorders	Hirsutism	Acne, alopecia	Eczema, increased sweating, rosacea
Musculoskeletal and connective tissue disorders			Arthritis
Reproductive system and breast disorders		Breast pain	Breast cyst, clitoral engorgement, enlarged clitoris, genital pruritus, vaginal burning sensation
General disorders and administration site conditions	Application site reaction (erythema, itching)		Anasarca, asthenia, chest tightness, chest discomfort
Investigations		Increased weight	Abnormal blood fibrinogen, increased heart rate, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, abnormal liver function test, increased blood triglycerides

4.9 Overdose

The mode of administration of Livensa makes overdose unlikely. Removal of the patch results in a rapid decrease in serum testosterone levels (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, androgens, ATC code: G03BA03

Mechanism of action
Testosterone, the primary circulating androgen in women, is a naturally occurring steroid, secreted by the ovaries and adrenal glands. In premenopausal women, the rate of production of testosterone is 100 to 400 micrograms/24 hours, of which half is contributed by the ovary as either testosterone or a precursor. Serum levels of androgens fall as women age. In women, who have undergone bilateral oophorectomy, serum levels of testosterone decline by approximately 50 % within days after surgery.

Livensa is a transdermal therapy for HSDD, which improves sexual desire while achieving testosterone concentrations compatible with premenopausal levels.

Clinical efficacy and safety
Two multi-centre, double-blind, placebo-controlled six month studies in 562 (INTIMATE SM1) and 533 (INTIMATE SM2) oophorectomised and hysterectomised women (surgically induced menopause), aged 20 to 70 years, with HSDD on concomitant estrogen were used to evaluate the efficacy and safety of Livensa. Total satisfying sexual activity (primary endpoint), sexual desire, and distress associated with low sexual desire (secondary endpoints) were evaluated with validated instruments.

In the combined study analysis at 24 weeks, the difference in the mean frequency of total satisfying episodes between Livensa and placebo was 1.07 per 4 weeks.

A significantly higher percentage of women who received Livensa reported a benefit in the three endpoints, that they considered clinically meaningful compared to women who received placebo. In the combined phase III data, excluding patients taking oral CEE, in whom there was no significant improvement in sexual function, 50.7 % of women (n=274) treated with Livensa and 29.4 % of those treated with placebo (n=269) were responders with regard to total satisfying sexual activity (primary endpoint), when a responder was predefined as having an increase in the 4-week frequency of satisfying activities of > 1.

Effects of Livensa were observed at 4 weeks after initiation of therapy (the first measured time point) and at all monthly efficacy time points thereafter.

Efficacy versus placebo was significant across a range of subgroups which included patients separated by the following baseline characteristics: age (all subgroups up to age 65 years); body weight (up to 80 kg) and oophorectomy (up to 15 years ago).

Subgroup analyses suggested that the route and type of concomitant estrogen (transdermal oestradiol, oral conjugated equine estrogen (CEE), oral non-CEE) can influence patient response. A responder analysis of the pivotal phase II and III studies showed significant improvements in all three major clinical endpoints versus placebo in patients on concomitant transdermal and oral non-CEE estrogens. However, the subgroup of patients receiving oral CEE did not demonstrate a significant improvement in sexual activity compared to placebo (see sections 4.2 and 4.4).

5.2 Pharmacokinetic properties

Absorption
Testosterone from Livensa is transported across intact skin by a passive diffusion process that is primarily controlled by permeation across the stratum corneum. Livensa is designed to systemically deliver 300 micrograms/day. Following application of the patch on abdominal skin, maximum serum concentrations of testosterone are reached within 24-36 hours, with a wide inter-individual variability. Serum concentrations of testosterone attain steady-state by the application of the second patch when applied in a twice-a-week regimen. Livensa did not influence serum concentrations of sex hormone binding globulin (SHBG), estrogens or adrenal hormones.

Serum concentrations of testosterone and SHBG in patients receiving Livensa in clinical safety and efficacy studies

Hormone	Baseline		Week 24		Week 52	
	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)
Free testosterone (pg/ml)	544	0.92 (0.03)	412	4.36 (0.16)	287	4.44 (0.31)
Total testosterone (ng/dl)	547	17.6 (0.4)	413	79.7 (2.7)	288	74.8 (3.6)
DHT (ng/dl)	271	7.65 (0.34)	143	20.98 (0.98)	169	21.04 (0.97)
SHBG (nmol/l)	547	91.7 (2.5)	415	93.9 (2.8)	290	90.0 (3.6)

DHT = dihydrotestosterone, SHBG = sex hormone binding globulin
SEM = Standard Error of the Mean

Distribution
In women, circulating testosterone is primarily bound in the serum to SHBG (65-80 %) and to albumin (20-30 %) leaving only about 0.5-2 % as the free fraction. The affinity of binding to serum SHBG is relatively high and the SHBG bound fraction is regarded as not contributing to biological activity. Binding to albumin is of relatively low affinity and is reversible. The albumin-bound fraction and the unbound fraction are collectively termed 'bioavailable' testosterone. The amount of SHBG and albumin in serum and the total testosterone concentration determine the distribution of free and

bioavailable testosterone. Serum concentration of SHBG is influenced by the route of administration of concomitant estrogen therapy.

Biotransformation
Testosterone is metabolised primarily in the liver. Testosterone is metabolised to various 17-ketosteroids and further metabolism results in inactive glucuronides and other conjugates. The active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). DHT has a greater affinity to SHBG than does testosterone. DHT concentrations increased in parallel with testosterone concentrations during Livensa treatment. There were no significant differences in serum estradiol and estrone levels in patients treated with Livensa for up to 52 weeks compared to baseline.

On removal of an Livensa patch, testosterone serum concentrations return to near baseline values within 12 hours due to its short terminal exponential half-life (approximately 2 hours). There was no evidence of accumulation of testosterone over 52 weeks of treatment.

Elimination
Testosterone is mainly excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites.

5.3 Preclinical safety data

Toxicological studies of testosterone have only revealed effects which can be explained based on the hormone profile.

Testosterone has been found to be nongenotoxic. Non-clinical studies on a relationship between testosterone treatment and cancer suggest that high doses may promote tumour growth in sex organs, mammary glands and liver in laboratory animals. The significance of these data for the use of Livensa in patients is not known.

Testosterone has a masculinising effect on female rat foetuses when dosed subcutaneously at 0.5 or 1 mg/day (as the propionate ester) to pregnant rats during organogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer
Translucent polyethylene backing film
Printing ink
sunset yellow FCF (E110)
latolrubine BK (E180)
copper phthalocyanine blue pigment.

Self adhesive matrix drug layer
Sorbitan oleate
Acrylic co-polymer adhesive containing 2-Ethylhexylacrylate – 1-Vinyl-2-pyrrolidone co-polymer.

Protective release liner
Siliconised polyester film

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

Each patch is packed in a sealed laminated sachet. The sachet material comprises of food grade paper/LDPE/aluminium foil/ethylene methacrylic acid copolymer (outer to inner layer). The ethylene methacrylic acid copolymer (Surlyn) is the heat seal layer which allows the two laminate sachet stocks to be heat-sealed together to form the sachet.
Cartons of 2, 8 and 24 patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The transdermal patch should not be flushed down the toilet.

The used patch should be folded in half, sticking the patch to itself, and discarded in a safe way in order to keep it away from children (e.g in a rubbish bin).

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Warner Chilcott Deutschland GmbH
Dr.-Otto-Röhm-Strasse 2-4
64331 Weiterstadt
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/351/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28-July-2006
Date of latest renewal: 28-July-2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Warner Chilcott Deutschland GmbH
Dr.-Otto-Röhm-Strasse 2-4
64331 Weiterstadt
Germany

Warner Chilcott France
Parc d'activité de la Grande Brèche
5 rue Désir Prévost
91070 Bondoufle
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.
The MAH will continue to submit 6 monthly PSURs unless otherwise specified by CHMP.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) dated 19-September-2010, presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (Box of 2, 8 or 24 patches)

1. NAME OF THE MEDICINAL PRODUCT

Livensa 300 micrograms/24 hours transdermal patch
Testosterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 patch of 28 cm^2 contains 8.4 mg of testosterone and provides 300 micrograms per 24 hours

3. LIST OF EXCIPIENTS

Also contains: Sorbitan oleate, 2-Ethylhexylacrylate – 1-Vinyl-2-pyrrolidone copolymer, E110, E180, copper phthalocyanine blue pigment, polyethylene, siliconised polyester film.

4. PHARMACEUTICAL FORM AND CONTENTS

2 transdermal patches
8 transdermal patches
24 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Apply immediately upon removal from the sachet.

Read the package leaflet before use.

Transdermal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Warner Chilcott Deutschland GmbH
Dr.-Otto-Röhm-Strasse 2-4
64331 Weiterstadt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/351/001-003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Livensa

Tuck flap here to close.

Information to appear on the inside of the flap

When to apply the patch:
The patch needs to be changed twice weekly. Choose your two days and tick the box. Change the patch only on these two days.

- Sunday + Wednesday
- Monday + Thursday
- Tuesday + Friday
- Wednesday + Saturday
- Thursday + Sunday
- Friday + Monday
- Saturday + Tuesday

Continue to use for as long as your doctor prescribes.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Livensa 300 micrograms/24 hours transdermal patch
Testosterone
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

1 patch of 28 cm^2 contains 8.4 mg of testosterone and provides 300 micrograms per 24 hours.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Livensa 300 micrograms/24 hours transdermal patch
Testosterone

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT LIVENSA IS AND WHAT IT IS USED FOR

Livensa is a transdermal patch which constantly releases small amounts of testosterone that is absorbed through your skin into the bloodstream. The testosterone in Livensa is the same hormone as that produced naturally in men and women.

After removal of the ovaries, testosterone drops to half of the levels compared to before the operation. Decrease in testosterone has been associated with low sexual desire, reduced sexual thoughts and reduced sexual arousal. All or any of these problems can cause personal distress or relationship difficulties. The medical term for this condition is Hypoactive Sexual Desire Disorder, also known as HSDD.

Livensa is used to treat HSDD.
Livensa is intended for use by women up to the age of 60 years who:
- have a low sexual desire which is causing distress or concern, and
- have had both of their ovaries removed, and
- have had their womb removed (hysterectomy), and
- are receiving estrogen therapy.

It may take longer than one month for you to notice an improvement. If you have not experienced a positive effect of Livensa within 3-6 months, you should inform your doctor, who will suggest that treatment be discontinued.

2. BEFORE YOU USE LIVENSA

Do not use Livensa
- if you are allergic (hypersensitive) to testosterone or any of the other ingredients of Livensa (see section 'Further information' at the end of this leaflet).
- if you know that you have had in the past, currently have, or think that you might have, breast cancer or any other cancer which your doctor has described as being caused or stimulated by the female hormone estrogen, also called 'estrogen-dependent' cancers.
- if you have other conditions that your doctor may consider not appropriate for the use of estrogen and/or testosterone.

Take special care with Livensa
- if you have a history of heart, liver or kidney disease. Oedema may be a serious complication from high doses of testosterone, however, this is not expected from low dose of testosterone delivered by the Livensa patch.
- if you have cancer of the lining of the womb (endometrial cancer), be aware that there is little information available on the effects of testosterone on the lining of the womb (endometrium).
- if you are diabetic, as testosterone may lower blood glucose levels.
- if you have a history of excessive adult acne, body or facial hair, hair loss, enlargement of the clitoris or voice deepening or hoarseness.

If you have any of the above, tell your doctor before you start to use Livensa. Your doctor will advise you on what you should do.

The efficacy of Livensa is reduced if your estrogen therapy is of a certain type ('conjugated equine estrogens'). Therefore, you need to discuss your type of estrogen with your doctor, who could advise you which type of estrogen is suitable together with Livensa.

If you stop estrogen therapy you must also stop using Livensa. Keep in mind that estrogens should be administered for the shortest possible duration.

Use Livensa only as long as you experience a positive effect of the treatment. There is no information on the safety of Livensa beyond 12 months.

There are limited data about the use in women above the age of 60. Livensa is intended for use by women up to the age of 60 years who have had both their ovaries and their womb removed.

It is not known whether Livensa increases the risk of breast cancer and endometrium cancer. Your doctor will carefully monitor you with regard to breast cancer and endometrium cancer.

Children and adolescents
Livensa is not for use in children and adolescents.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Tell your doctor if you are taking blood-thinning (anticoagulant) treatment.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Livensa is only indicated for women in their menopause after the ovaries and uterus have been removed. Do not use Livensa if you are, or suspect that you may be pregnant or are able to become pregnant, because it may cause harm to the unborn child.
Do not use Livensa in case of breast-feeding because it may cause harm to the child.

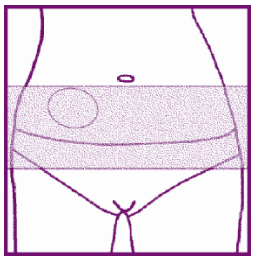
Driving and using machines
You can drive and use machines while using Livensa.

3. HOW TO USE LIVENSA

Always use Livensa exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure of the instructions or if you want any more information. The usual dose is one patch twice weekly (each 3 to 4 days), see below 'How and when to change your patch'. The active substance is released from the patch constantly over 3 to 4 days (corresponding to 300 micrograms per 24 hours) and is absorbed through your skin.

Where to stick the patch

- Stick the patch onto your **lower abdomen,** below your waist. **Do not** stick the patch on the breasts or bottom.



Make sure that your skin at the application site is:

- ✓ clean and dry (free of lotions, moisturisers, and powders)
- ✓ as smooth as possible (no major creases or skin folds)
- ✓ not cut or irritated (free of rashes or other skin problems)
- ✓ unlikely to be rubbed by clothing excessively
- ✓ preferably free from hair.

- When changing your patch, stick the new patch on to a **different area** of the skin **of your abdomen**, otherwise you are more likely to cause skin irritation.

- Only **one** patch is to be worn at a time.

- If you are also using estrogen patches, make sure that the Livensa patch and the estrogen patch do not overlap.

- For at least one week after removing a patch, do not place a new patch in the same area.

How to stick on the patch

Step 1 Tear open the sachet. Do not use scissors as you may accidentally damage the patch. Remove the patch. Apply the patch immediately after removing it from the sachet.

Step 2 While holding the patch, remove half of the protective liner that covers the sticky part of the patch. Avoid touching the sticky side of the patch with your fingers.

Step 3 Apply the sticky side of the patch to the selected area onto your skin. Press the sticky side of the patch firmly into place for about 10 seconds.

Step 4 Fold back the patch and carefully remove the other half of the liner. Press the entire patch firmly against your skin with the palm of your hand for about 10 seconds. Use your fingers to make sure the edges of the patch stick to the skin. If an area of the patch lifts, apply pressure to that area.

How and when to change your patch

- You will need to change your patch every 3 to 4 days, which means using **two patches each week**. This will mean that you wear one patch for 3 days and the other for 4 days. Decide which two days each week you are going to change your patch and change the patch on the same two days each week.

  For example: If you decide to start treatment on a Monday, then you have to change your patch always on a Thursday and a Monday.

  - o Sunday + Wednesday
  - ✓ Monday + Thursday
  - o Tuesday + Friday
  - o Wednesday + Saturday
  - o Thursday + Sunday
  - o Friday + Monday
  - o Saturday + Tuesday

  As a reminder, mark on the outer carton your chosen patch-change days.

- On the patch-change day, remove the used patch and immediately stick the new patch on to a **different area** of skin **of your abdomen**. Continue your treatment for as long as your doctor advises.

- Fold the used patch in half, sticking the patch to itself, and discard it in a safe way in order to keep it away from children (e.g. in a rubbish bin). Medicines should not be disposed of via wastewater (do not flush it down the toilet). Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

What about showering, bathing and exercising?

You may shower, bath, swim and exercise as normal while wearing the patch. The patch is designed to remain in place during these times. However, do not scrub the area where the patch has been placed too hard.

What about sunbathing?

Always make sure your patch is covered by clothing.

What if your patch becomes loose, lifts at the edges or falls off?
If a patch does begin to come off, you may be able to make it stick again by pressing on it firmly. If you cannot get the patch to stick successfully, remove the loose patch and use a new patch. Then continue with your regular schedule of patch-change days, even if this means discarding a patch after you have worn it for less than 3-4 days.

If you use more patches than you should
If you have applied more than one patch at a time
Remove **all the patches** sticking on to your skin and consult your doctor or pharmacist for further information on how to continue treatment with Livensa. Overdosing with Livensa is unlikely when used as directed, because once the patch is taken off testosterone is quickly removed by the body.

If you forget to use a patch
If you forget to change your patch
Change your patch as soon as you remember, and then continue with your regular schedule of patch-change days, even if this means discarding a patch after you have worn it for less than 3-4 days. Returning to your regular schedule will help you remember when to change your patch.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Livensa can cause side effects, although not everybody gets them.

Tell your doctor **immediately:**
- if you experience hair loss (a common side effect which may affect up to 1 in 10 people), enlargement of the clitoris (an uncommon side effect which may affect up to 1 in 100 people), an increase in the amount of hair on the chin or upper lip (a very common side effect which may affect more than 1 in 10 people), voice deepening or hoarseness (a common side effect), although these side effects may be mild. They are usually reversible if Livensa treatment is discontinued.

  You should self assess for increased acne (a common side effect), increased hair growth on your face, loss of hair, deepening of your voice or enlargement of your clitoris, which all could be signs of side effects of testosterone, which is the active substance in Livensa.

- if you notice any skin reactions at the site of application (a very common side effect) such as redness, oedema, or blistering. In case of severe application site reaction, the treatment should be discontinued.

Other common side effects
Most of them are mild in nature and reversible.
- migraine
- insomnia/inability to sleep properly
  breast pain
  weight gain
- stomach pain

Other uncommon side effects
Most of them are mild in nature and reversible.
- sinusitis (inflammation of nasal sinus)
- abnormal clotting factor
- hypersensitivity (allergic reactions)
- increased appetite
- agitation

- anxiety
- disturbance in attention
- dysgeusia (distorted sense of taste)
- impaired balance
- hyperaesthesia (abnormal increase in sensitivity to stimuli of the senses)
- oral paraesthesia (tingling or numb sensation in the mouth)
- transient ischemic attack (mini stroke)
- diplopia (double vision)
- eye redness
- palpitations (rapid and irregular heart beat)
- nasal congestion
- throat tightness
- diarrhoea
- dry mouth
- nausea
- eczema
- increased sweating
- rosacea (redness of the face)
- arthritis
- breast cyst
- clitoral engorgement
- genital pruritus (genital itching sensation)
- vaginal burning sensation
- anasarca (widespread swelling of the skin)
- asthenia (lack of energy and strength)
- chest tightness
- chest discomfort
- abnormal blood fibrinogen (abnormal blood clotting)
- increased heart rate
- increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, abnormal liver function test, increased blood triglycerides (all measures of liver function).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE LIVENSA

- Keep out of the reach and sight of children
- Do not use Livensa after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Do not refrigerate or freeze.
- Medicines should not be disposed of via wastewater (do not flush it down the toilet) or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Livensa contains
The active substance is testosterone. Each patch contains 8.4 mg of testosterone, releasing 300 micrograms of testosterone over 24 hours.

The other ingredients are: Sorbitan oleate, 2-Ethylhexylacrylate – 1-Vinyl-2-pyrrolidone co-polymer.
Backing layer

Translucent polyethylene backing film printed with ink containing sunset yellow FCF (E110), latolrubine BK (E180) and copper phthalocyanine blue pigment.
Protective release liner
Siliconised polyester film.

What Livensa looks like and contents of the pack
Livensa is a thin, clear, oval patch with T001 stamped on the back.
Each patch is sealed in a sachet.
The following pack sizes are available: 2, 8 and 24 patches. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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64331 Weiterstadt
Germany

Warner Chilcott France
Parc d'activité de la Grande Brèche
5 rue Désir Prévost
91070 Bondoufle
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Livensa remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

The off-label use is a safety risk. It is a CHMP concern that the data from the THIN (The Health Improvement Database) study suggests that approx 70% of the users are outside indication.

The CHMP decided that the MAH should continue to submit 6 monthly PSURs.

Therefore, based on the safety profile in Livensa, which requires the submission of 6 monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.