Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tibolone Teva 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains as active substance 2.5mg of tibolone.

Excipient: 86mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, flat bevelled edge tablets, coded “TIB” on one side and “2.5” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after menopause.

Second line therapy for prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

There is limited experience in treating women over age 65 years.

4.2 Posology and method of administration

Adults and the elderly
The dosage is one tablet per day without interruption. No dose adjustment is necessary for the elderly. Tibolone tablets should be swallowed without chewing, with some water or other drink, preferably at the same time of day. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

A separate progestogen should not be added with Tibolone treatment.

Tibolone is contraindicated in patients with impaired liver function (see section 4.3).

Starting Tibolone

- Women experiencing a natural menopause should commence treatment with Tibolone at least 12 months after their last natural bleed.

- Women experiencing a surgical menopause may commence treatment with Tibolone immediately.

Switching from a sequential or continuous-combined HRT Preparation
If changing from a Sequential HRT preparation, treatment with Tibolone should start the day following completion of the prior regimen.
If changing from a Continuous-combined HRT preparation, treatment can start at any time.

Any irregular/unscheduled vaginal bleeding, either on or off HRT, for which there is no obvious cause, should be investigated before starting Tibolone (see section 4.3).

Missed pills
A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case, the missed dose should be skipped and the next dose should be taken at the normal time. Missing a dose may increase the likelihood of breakthrough bleeding and spotting.

Children
Not applicable.

4.3 Contraindications

Known hypersensitivity to the active substance or any of the excipients.
Known, past or suspected breast cancer.
Known or suspected estrogen – dependent malignant tumours (e.g. endometrial cancer).
Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism).
Any history of arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke or TIA);
Undiagnosed vaginal bleeding.
Untreated endometrial hyperplasia.
Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.
Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as benefit outweighs the risk.

Medical Examination/follow-up
Before initiating or reinstituting Tibolone, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (See 'Breast cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Tibolone, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache

- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued when a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Any other situation described in the section 4.3.

Endometrial hyperplasia and cancer

– The endometrial safety of tibolone is currently uncertain.

– Two large UK population-based observational studies, The Million Women Study (MWS) and a General Practice Research Database (GPRD) study, have reported an increased risk of endometrial cancer in women who had used tibolone compared with combined HRT and never-users (see section 4.8). The risk increased with increasing duration of use.

– The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The addition of a progestogen to estrogen-only HRT for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk (see section 4.8).

– Break-through bleeding and spotting may occur during the first months of treatment (see section 5.1). Women should be advised to report any break-through bleeding or spotting if it is still present after 6 months of treatment, if it starts beyond that time or continues after treatment has been discontinued. The woman should be referred for gynaecological investigation which is likely to include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

– A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogens or estrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

– In the MWS, the relative risk of breast cancer diagnosis with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of the type of progestogen. There was no evidence of a difference in risk between the different routes of administration. The risk of breast cancer associated with tibolone was lower than the risk associated with estrogen plus progestogen combined HRT, but higher than the risk associated with estrogen-only therapy.

– In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

- HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two--to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later. It is unknown whether tibolone carries the same level of risk.

- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement. Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products, or tibolone.

Stroke

- One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate =1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products, or tibolone.

- Preliminary results of a randomized double-blind placebo-controlled study (LIFT study, N = 4538) on the efficacy of low dose (1.25mg) tibolone (N = 2267) for the treatment of osteoporosis in elderly women (mean age 68 years), has shown an increased risk of stroke compared to placebo after an average of 2.75 years of follow-up. The incidence of strokes observed in the placebo and tibolone arms was 1.8 and 4.1 per 1000 women-years respectively, a difference of approximately 11.5 extra cases per 1000 women over a 5 year period, corresponding to a relative risk of 2.3 (p=0.02).

Ovarian cancer

- Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT or tibolone, confers a different risk than estrogen-only products.

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

- Treatment with tibolone results in a very minor decrease in thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. Tibolone decreases the level of sex-hormone-binding globulin (SHBG) whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.

- Tibolone is not intended for contraceptive use.

- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined conjugated estrogens and medroxyprogesterone acetate after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products, or tibolone.

- 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

The information regarding interactions between tibolone and other medicinal products is limited. The effect of inhibition or induction of the metabolism of tibolone has not been studied. Due to the complex profile with different metabolites contributing to different pharmacological effects, the effects of an interaction are difficult to predict. However, the following potential interactions should be considered on a theoretical basis:

Enzyme inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus affect its therapeutic effect.

Herbal preparations containing St. John`s Wort (Hyperuricum Perforatum) may induce the metabolism of oestrogens and progestagens. Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Since tibolone may increase blood fibrinolytic activity (lower fibrinogen levels, higher antithrombin III, plasminogen and fibrinolytic activity values) it may enhance the effect of anticoagulants, such as warfarin. Therefore, the simultaneous use of tibolone and warfarin should be monitored, especially when starting or stopping concurrent tibolone treatment, and the warfarin dose should be appropriately adjusted.

An in vivo study showed that tibolone moderately affected the pharmacokinetics of the CYP3A4 substrate midazolam and based on this, interactions with other CYP3A4 substrates may also be expected.

In vitro data indicate that tibolone and its metabolites can inhibit the cytochrome P450 isoenzyme 2C9. Caution is therefore advised if tibolone is combined with medicinal products metabolised via CYP2C9, especially those with a narrow therapeutic range, e.g. warfarin, phenytoin and tolbutamide.

4.6 Fertility, pregnancy and lactation

Tibolone is not indicated during pregnancy. If pregnancy occurs during medication with Tibolone, treatment should be withdrawn immediately. For tibolone no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tibolone is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Tibolone is not known to have any effects on alertness and concentration.

4.8 Undesirable effects

Clinical Trials Experience

This section describes undesirable effects, which were registered in 16 placebo controlled studies, with 1463 women receiving therapeutic doses of tibolone, and 855 women receiving placebo. The duration of treatment in these studies ranged from 2 to 24 months. The following undesirable effects occurred statistically significantly more frequently during treatment with tibolone than with placebo.

Frequencies are defined as: common (≥1/100 to <1/10), uncommon (≥1/1000 to ≤1/100).

Table 1 *Undesirable effects of Tibolone*

System organ class	*Common (≥ 1/100,<1/10)*	*Uncommon (≥ 1/1000 to ≤ 1/100)*
Metabolism and nutrition disorders	*Weight Increase*	
Nervous system disorders		*Amnesia*
Gastrointestinal disorders	*Abdominal pain*	
Skin and subcutaneous tissue disorders	*Hypertrichosis*	
Reproductive system and breast disorders	*Vaginal bleeding or spotting* *Leukorrhoea*	

	Breast pain *Genital pruritus* *Genital moniliasis* *Vaginitis*	

During post-marketing use, the above mentioned undesirable effects were observed as well as some other undesirable effects, such as dizziness, rash, pruritus, seborroic dermatitis, headache, migraine, visual disturbances (including blurred vision), gastric and intestinal irritation, depression, oedemas, effects on the musculoskeletal system as e.g. joint or muscle pain and change in liver functions. It was demonstrated in clinical studies, that the latter named did not occur statistically more often in tibolone-treatment compared with placebo.

Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with the number of years of HRT use in current or recent HRT users.

For *estrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was estrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95% CI 1.21 – 1.49) and 1.30 (95% CI 1.21 – 1.40), respectively.

For *estrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, compared to never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI: 1.88 – 2.12) than use of estrogens alone (RR = 1.30, 95% CI: 1.21-1.40) or use of tibolone (RR=1.45; 95% CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95% CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be

  For users of *estrogen-only* replacement therapy
  - between 0 and 3 (best estimate = 1.5) for 5 years use
  - between 3 and 7 (best estimate = 5) for 10 years use

  For users of estrogen plus progestogen combined HRT
  - between 5 and 7 (best estimate =6) for 5 years use
  - between 18 and 20 (best estimate =19) for 10 years use

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *estrogen plus progestogen* combined HRT (CEE + MPA) per 10,000 women years.
According to calculations from the trial data, it is estimated that:

For 1000 women in the placebo group,
- about 16 cases of invasive breast cancer would be diagnosed in 5 years.

For 1000 women who used *estrogen-progestogen* combined HRT (CEE + MPA), the number of *additional* cases would be,
- between 0 and 9 (best estimate = 4) for 5 years use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer
There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with tibolone. The MWS has estimated an increased risk of endometrial cancer in women who had used tibolone compared with never users of HRT (RR approximately 1.8, 95% CI 1.4 - 2.3). The risk increased with increasing duration of use.
The GPRD study has estimated an increase in the risk of endometrial cancer in women who use tibolone compared with those who used combined sequential HRT (RR approximately 1.5, 95% CI, 1.0 – 2.3).

Other adverse reactions reported in association with estrogen-progestogen treatment are:

- Estrogen-dependent neoplasms benign and malignant;
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see sections 4.3 and 4.4;
- Myocardial infarction and stroke;
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
- Probable dementia (see section 4.4).

Stroke
The LIFT-study has estimated a 2.3-fold increased risk of stroke in women (mean age 68 years) using 1,25 mg tibolone compared with placebo (RR 2,3, p=0,02). The absolute risk increase is 2.3 strokes per 1000 women treated per year. See section 4.4.

4.9 Overdose

The acute toxicity of tibolone in animals is very low. Therefore toxic symptoms are not expected to occur even when several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other estrogens
ATC code: G03CX01

After oral administration tibolone is rapidly metabolised into three compounds which all contribute to the pharmacological effects of tibolone. Two of these metabolites (3α-OH-tibolone and 3β-OH–tibolone) have predominantly estrogenic activity, whereas the third metabolite (Δ4-isomer of tibolone) and the parent compound have predominantly progestogenic and androgenic activities.
Tibolone substitutes for the loss of estrogen production in postmenopausal women, and alleviates menopausal symptoms. Tibolone prevents bone loss following menopause or ovariectomy.

In vitro studies suggest that tibolone is subject to tissue-selective local metabolism, with the Δ4-isomer mainly formed in endometrial tissue. In the breast, tibolone inhibits the sulfatase enzyme thereby reducing the levels of the 3-OH – tibolone metabolites produced in this tissue. The clinical relevance of these studies is not known (see section 4.8).

Clinical trial information on tibolone:

- Relief of estrogen-deficiency symptoms
  - Improvement of symptoms generally occurs within a few weeks

- Effects on the endometrium and bleeding patterns

  – There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with tibolone.

  – Amenorrhea (no bleeding or spotting) was seen in 88.4% of the women during months 10-12 of tibolone treatment. Break through bleeding and/or spotting appeared in 32.6% of the women during the first three months of treatment and in 11.6% during months 10-12 of treatment.

- Prevention of osteoporosis

  – Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.
  – Protection appears to be effective for as long as treatment is continued.
  – After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women. After 2 years of treatment with tibolone, the increase in lumbar spine bone mineral density (BMD) was 2.6 ± 3.8%. The percentage of women who maintained or gained BMD in lumbar zone during treatment was 76%. A second study confirmed these results.
  – Tibolone also had an effect on hip BMD. In one study, the increase after 2 years was 0.7 ± 3.9% at the femoral neck and 1.7 ± 3.0% at the total hip. The percentage of women who maintained or gained BMD in the hip region during treatment was 72.5%. A second study showed that the increase after 2 years was 1.3 ± 5.1 % at the femoral neck and 2.9 ± 3.4% at the total hip. The percentage of women who maintained or gained BMD in the hip region during treatment was 84.7%.

- Effects on the breast
  – Data from clinical studies suggest that mammographic density is not increased in women treated with tibolone compared to placebo.

5.2 Pharmacokinetic properties

Following oral administration tibolone is rapidly and extensively absorbed.
The consumption of food has no significant effects on the extent of absorption.
Due to rapid metabolism the plasma levels of tibolone are very low. The plasma levels of the Δ4-isomer of tibolone are also very low. Therefore some of the pharmacokinetic parameters could not be determined. Peak plasma levels of the 3α-OH and the 3β-0H metabolites are higher but accumulation does not occur.

Table 2: Pharmacokinetic parameters of Tibolone

	tibolone		3α-OH metabolite		3β-0H metabolite		Δ4-isomer	
	SD	MD	SD	MD	SD	MD	SD	MD
C_{max} (ng/ml)	1.37	1.72	14.23	14.15	3.43	3.75	0.47	0.43
$C_{Average}$	---	---	---	1.88	---	---	---	---
T_{max}(h)	1.08	1.19	1.21	1.15	1.37	1.35	1.64	1.65
$T_{1/2}$(h)	---	---	5.78	7.71	5.87	---	---	---
C_{min} (ng/ml)	---	---	---	0.23	---	---	---	---
Auc_{0-24} (ng/ml.h)	---	---	53.23	44.73	16.23	9.20	---	---

SD = Single Dose; MD = Multi Dose

Excretion of tibolone is mainly in the form of conjugated (mostly sulfated) metabolites. Part of the administered compound is excreted in the urine, but most is eliminated via the faeces.

The pharmacokinetic parameters for tibolone and its metabolites were found to be independent of renal function.

5.3 Preclinical safety data

Tibolone is not genotoxic. The results of animal studies of repeated-dose toxicity and carcinogenesis were in agreement with the expected effects of high-dose sex steroids, especially estrogens**.** Furthermore, a carcinogenic effect on non-hormone-dependent tissues was seen in certain strains of rat (hepatic tumours) and mouse (bladder tumours), the relevance of this evidence to man is uncertain.

In animal studies, tibolone had anti-fertility and embryotoxic activities by virtue of its hormonal properties. Tibolone was not teratogenic in mice and rats. It displayed teratogenic potential in the rabbit at near-abortive dosages. (See section 4.6)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize starch pregelatinized
Ascorbyl Palmitate (E304)
Sodium citrate
Sodium laurilsulfate
Croscarmellose Sodium
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

PVC-PVDC /Aluminium foil blisters in pack sizes of 28, 30, 60, 84 and100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/45/1

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