

Public Assessment Report

Tibolone 2.5mg Tablets

PL 00530/0708 PL 00530/0770 PL 00530/0771

PL 00530/0708 PL 00530/0770 PL 00530/0771

UKPAR

TABLE OF CONTENTS

	Page
Lay Summary	3
Scientific discussion	4
Steps taken for assessment	24
Steps taken after authorisation – summary	25
Summary of Product Characteristics	26
Patient Information Leaflets	65
Labelling	69

PL 00530/0708 PL 00530/0770 PL 00530/0771

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Norton Healthcare Limited (trading as Ivax Pharmaceuticals UK Limited) Marketing Authorisations (licences) for the medicinal product Tibolone 2.5mg Tablets (PLs 00530/0708, 0770-1). This is a prescription only medicine [POM] used to relieve the symptoms of menopause. It can also be used to prevent thinning of the bones (known as osteoporosis) in those who are at high risk of future fractures but cannot take other medicines for this purpose.

This product contains the active ingredient tibolone which belongs to a group of medicines called hormone replacement therapy (HRT). However, unlike most other HRTs that are actual hormones, tibolone is broken down in the body to produce hormones.

The clinical data presented to the MHRA, before licensing, demonstrated that Tibolone 2.5mg Tablets is essentially similar or equivalent to the approved product, Livial 2.5mg Tablets, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these three identical applications and it was decided that the benefits of using Tibolone 2.5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

PL 00530/0708 PL 00530/0770 PL 00530/0771

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

	Page
Introduction	5
Pharmaceutical assessment	6
Preclinical assessment	14
Clinical assessment	15
Overall conclusions and risk benefit assessment	23

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Tibolone 2.5mg Tablets (PLs 00530/0708, 0770-1) to Norton Healthcare Limited (trading as Ivax Pharmaceuticals UK Limited) on 10 April 2006. The product is a prescription only medicine.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, as amended, claiming essential similarity to Livial 2.5mg Tablets (PL 00065/0086), granted 5 March 1991.

This product contains the active ingredient tibolone and is indicated for use in the treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after the menopause, and in the prevention of osteoporosis in postmenopausal women at high risk of future fractures when other treatments for this indication are considered unsuitable (eg, in the case of intolerance or contraindications).

Tibolone is rapidly metabolised into three compounds which all contribute to its pharmacological effects. Two of these metabolites (3α -OH-tibolone and 3β -OH-tibolone) have predominantly estrogenic activity, whereas the third metabolite (Δ 4-isomer of tibolone) and the parent compound have predominantly progestogenic and androgenic activities.

PHARMACEUTICAL ASSESSMENT

PL Number: PLs 00530/0708, 0770-1 Name of Product: Tibolone 2.5mg Tablets

Actives: Tibolone

Company Name: Norton Healthcare Ltd (T/A Ivax Pharmaceuticals UK)

E.C. Directive: 2001/83/EC Article 10.1(a)(iii)

Legal Status: POM

INTRODUCTION

Legal basis

These are national abridged applications for Tibolone 2.5mg Tablets, submitted under Article 10.1(a)(iii), as amended, claiming essential similarity to Livial 2.5mg Tablets (PL 00065/0086, granted 5 March 1991), marketed by Organon Laboratories Ltd., UK, also used in the bioequivalence study.

The fee category for PL 00530/0708 is complex abridged. This is accepted as the active substance tibolone is from a new source not previously approved in the UK licensed product. PLs 00530/0770-1 are duplicates of PL 00530/0708 and are assessed in parallel.

Use

The tablets are indicated for use in women only for the treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after the menopause, and prevention of osteoporosis in postmenopausal women at high risk of future fractures when other treatments for this indication are considered unsuitable (eg, in the case of intolerance or contraindications). The dosage is one tablet per day.

TSE

Confirmation has been provided that lactose monohydrate and spray dried lactose used in the tablet are derived from the milk of healthy cows, fit for human consumption. It is also confirmed that no animal derived materials, other than the calf rennet, are used.

Satisfactory TSE declarations have been provided for ascorbyl palmitate, tri-sodium citrate dihydrate and magnesium stearate (vegetable grade). Similar TSE statements for croscarmellose and pregelatinized starch have been supplied.

A satisfactory TSE statement is provided for the drug substance, tibolone.

The product is therefore Annex II according to MCA (now MHRA) letter dated 7 July 2000.

Background

There were no generic licences approved for tibolone.

The applications from Norton Healthcare Ltd. are presented in the Common Technical Document (CTD) format.

DRUG SUBSTANCE

A source of the active substance tibolone is proposed. The active from this source is not approved for use in a UK licence and is the subject of a drug master file. Full assessment of the DMF has been carried out.

A copy of the current DMF edition of the applicant's part has been provided in the CTD format. A letter of access is provided.

A drug substance specification is provided by the active ingredient manufacturer (AIM).

Control of drug substance

Specification

A satisfactory drug substance specification has been provided by the finished product manufacturer.

The specification meets the requirements of ICH guidelines, with respect to specifications for residual solvents (CPMP/ICH/283/95), and with the Ph.Eur. (4th Edition) General Monograph for Substances for Pharmaceutical Use, with respect to related substances.

Satisfactory Certificates of Analysis have been supplied.

Analytical procedures

Satisfactory analytical procedures are described.

Validation of analytical procedures

Validation protocols and reports for assay, related substances and residual solvents, generated by the AIM, are described.

Batch analysis

The results for the batches provided by the applicant are within specification. Certificates of Analysis from the AIM for batches of tibolone are also satisfactory.

Justification of specification

No pharmacopoeial monograph exists for tibolone. It is stated that the AIM has developed methods and specifications, based upon current guidelines. Standard pharmacopoeial tests and requirements are applied, where applicable.

Drug purity is established and related substances are controlled. The limits are set on the basis of laboratory, pilot scale-up batches and general pharmacopoeial references.

The limits applied for residual solvents are in line with ICH guidelines.

The methods used for the control of active substance are considered appropriate to guarantee the quality from batch to batch.

Reference standards

Satisfactory primary and working reference standards have been described. Certificates of Analysis are provided by the AIM.

Impurity standards used by the AIM are described. Certificates of Analysis are provided.

Container closure system

A satisfactory description has been provided by the applicant.

Stability of tibolone

The proposed shelf life is acceptable and based on satisfactory stability data provided for batches stored at ICH conditions.

DRUG PRODUCT

Composition of the medicinal product

The composition is given in the table below.

Ingredients	Reference
	Standard
Active ingredient	
Tibolone	In-house
Excipients	
Lactose monohydrate	Ph.Eur.
Starch pregelatinized	Ph.Eur.
Ascorbyl palmitate	Ph.Eur.
Tri-sodium citrate dihydrate	Ph.Eur.
Sodium lauryl sulphate	Ph.Eur.
Purified water (not present in final product)	Ph.Eur.
Lactose spray dried	Ph.Eur.
Croscarmellose sodium	Ph.Eur.
Magnesium stearate	Ph.Eur.

Container

Tibolone tablets are packed in PVC/PVdC Aluminium foil blister pack containing 28, 30, 60, 84 and 100 tablets.

Development pharmaceutics

The aim was to develop a stable tablet containing 2.5mg tibolone, pharmaceutically equivalent to the innovator product, Livial 2.5mg Tablets (Organon).

Drug substance

Tibolone is a crystalline material with poor flow properties and practically insoluble in water. It is a mixture of known polymorphs Form I and Form II. The particle size of the drug

substance is likely to be critical for a relatively low dose formulation and for dissolution due to low aqueous drug solubility.

Excipients

The excipients chosen for Tibolone 2.5mg Tablets are based on the public information available for the innovator product and development trials. The excipients are all pharmacopoeial grade and are routinely used in the pharmaceutical industry.

Formulation development

The applicant had established from the 1996 edition of *L'informatore Farmaceutico* (Italy) that Livial contains lactose, starch, ascorbyl palmitate and magnesium stearate as inactive ingredients and the product is manufactured by a direct compression process. The applicant characterised four batches of Livial 2.5mg tablets (UK) for physical attributes, including dissolution.

Excipients were selected for initial development on the basis of preformulation studies.

The formulation trials were carried out and evaluated for *in vitro* comparison of the innovator tablets. The formulation and process parameters were varied in the trials so as to match the drug release with that of the innovator product.

Dissolution

Comparative dissolution profiles are provided for the test product biobatch and the reference product biobatch. This is acceptable.

Pharmacokinetic studies

An *in vivo* biostudy (Protocol P020214) was performed. The study was conducted as an open label, randomised, two-way, crossover, single dose study to compare the oral bioavailability of Tibolone test product by Ivax with reference product Livial. The test product was manufactured to the proposed marketing formula and an acceptable batch size. Satisfactory Certificates of Analysis are provided for the biobatches.

Twenty-six healthy postmenopausal women volunteers were included in the bioequivalence study. The study medication (2.5mg tibolone as the test product or as Livial reference product) was administered under fasting conditions. The two treatment periods were separated by a washout period of 2 weeks.

Blood samples were taken just before the start of a dose and at 0.25, 0.5, 1.00, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24 hours post dose The sampling period is considered suitable. The ratio of $AUC_{o-t}/AUC_{o-\alpha}$ for the test and reference is around 0.89 for test and reference product, i.e. >0.80.

Plasma concentrations of tibolone were determined using a validated method.

The pharmacokinetic parameters (t_{max} , C_{max} , AUC_{o-t} and $AUC_{o-\alpha}$) were determined for the test and reference drugs. The two formulations were compared by ANOVA applied to log transformed data. Bioequivalence was demonstrated for the C_{max} and AUCs using 90% CI

around test/reference ratios. For the t_{max} , a non-parameteric method was used. The data are given below:

N=26	C _{max}	T_{max}	$T_{1/2}$	AUC _{o-t}	AUC _{o-α}	F (rel)
	(pg/ml)	(h)	(h)	(h.pg/ml)	(h.pg/ml)	based on
						AUCo-α
Test	1377	0.50	5.59	2636	2963	0.92
Product,	CV=44	(0.25-2.0)	CV=48	CV=57	CV=53	(0.63-1.32)
N01060						
Livial	1373	1.00	5.24	2935	3293	-
Reference	CV=51	(0.50-2.5)	CV=43	CV=45	CV=44	
product						
Point	1.00	NS*		0.90	0.90	
estimate**						
90% CI**	(0.88-1.15)			(0.84-0.96)	(0.84-0.96)	

^{*}Wilcoxon signed rank test

Based on $AUC_{o-\alpha}$ m the mean relative bioavailability (F rel) was 0.92. The bioavailability parameters ($AUC_{o-\alpha}$, AUC_{o-t} and C_{max}) were within the 90% CI limit of 0.80-1.25. Therefore, the two products are considered bioequivalent, in line with NfG CPMP/EWP/QWP/1401/98 "The Investigation of Bioavailability and Bioequivalence".

Container closure system

The container is the blister pack, PVC/PVdC Aluminium foil with heat seal lacquer.

Microbiological attributes

Not given. The microbiological attributes are controlled in the finished product specification to Ph.Eur. 5.1.4 category 3A and acceptable.

Compatibility

Not given, but can be inferred from the product stability data, and are acceptable.

Manufacture

GMP statement and manufacturing chain

A suitable site of manufacture, assembly, QC, storage, batch release and distribution is named. A satisfactory copy of a manufacturing licence issued by the Irish Medicines Board is provided. This site has been approved for the manufacture of other UK licensed solid products.

The site of distribution and batch release is Norton Healthcare UK, T/A Ivax Pharmaceuticals UK, Royal Docks, London E16 2QJ. Satisfactory copies of WL/530/1 and WI/530/I are provided.

^{**90%} geometric Confidence Interval using In-transformed data.

Description of the manufacturing process

A satisfactory formula, flow diagram and description of manufacture are provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place. The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. No process validation data are provided. The applicant will undertake this during the manufacture of the first three commercial batches. A satisfactory validation protocol is provided.

Satisfactory in-process batch data for the biobatch/stability batches have been provided. These data demonstrate homogeneity of blends/tablets and consistent manufacture.

Control of excipients

Excipients included in a pharmacopoeia

The list of excipients, complying with Ph.Eur. requirements are given under "Composition of the medicinal product" above. None of the excipients are TSE risk materials. Magnesium stearate is derived from vegetable sources.

For each excipient, satisfactory supplier Certificates of Analysis and tests carried out on receipt by the product manufacturer have been provided.

Control of drug product

Specifications

The finished product specifications (release and shelf life) for Tibolone 2.5mg Tablets are provided.

The range of specification tests comply with the ICH guideline Q6A and Ph.Eur. requirements for tablets.

The microbial contamination test and limits comply with Ph.Eur. monograph, 5.1.4 Category 3A

Analytical procedures

Satisfactory methodology and validation data are provided.

Batch data

Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed.

Characterisation of Impurities

This is satisfactory.

Reference samples

Primary and working reference standards are described. The Certificates of Analysis provided are considered satisfactory.

Container closure system

Satisfactory details of product construction, supplier's and in-house specifications and Certificates of Analysis are provided. Data are also provided confirming compliance with EU directives, FDA and BGA regulations.

Stability of drug product

Standard storage conditions

A shelf life of 24 months with no storage precautions is proposed.

Pilot scale batches manufactured at the proposed site are used in the stability studies. The samples are representative of the product to be marketed in the proposed pack and also in bulk container. The stability of the innovator product, Livial 2.5mg tablets, is also compared with the test product.

The stability programme complies with current ICH guidelines, NfG CPMP/QWP/122/02 "Stability Testing on Active Substances and Finished Products". The programme is to continue to confirm or extend the shelf life. The stability programme is satisfactory.

Comparative stability data with the innovator product is provided.

No significant change in moisture, dissolution and assay are reported for the proposed tablets stored up to 6 months at 25°C/60%RH, 30°C/60%RH and at 40°C/75%RH. The data are comparable to those for Livial.

The results support the proposed shelf life of 24 months with no conditions.

Bioanalytical methods and validation

Satisfactory methodology and validation data are provided.

QUALITY OVERALL SUMMARY

This is satisfactory.

ESSENTIAL SIMILARITY

The following data support essential similarity:

- a) Acceptable bioequivalence between test and reference product.
- b) Comparative dissolution profiles are provided for test and reference product.
- c) The related substances are consistent with the brand leader.
- d) The active substance conforms to the ICH guidelines.

The product is considered essentially similar to the reference product.

PRODUCT BRAND NAME

This is generic and considered satisfactory.

PRODUCT PARTICULARS

Summary of Product Characteristics

This is satisfactory.

Patient Information leaflet

A coloured mock-up is provided.

Labelling

Coloured mock-ups are provided for the carton and blister strip.

MARKETING AUTHORISATION APPLICATION FORMS

These are satisfactory.

CONCLUSION

Marketing authorisations may be granted for these products.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required.	

CLINICAL ASSESSMENT

PL Number: PLs 00530/0708, 0770-1 Name of Product: Tibolone 2.5mg Tablets

Actives: Tibolone

Company Name: Norton Healthcare Ltd (T/A Ivax Pharmaceuticals UK)

E.C. Directive: 2001/83/EC Article 10.1(a)(iii)

Legal Status: POM

INTRODUCTION

Type of application and aspects on development

These are national abridged generic applications submitted under Article 10.1(a)(iii) of Directive 2001/83/EC, as amended, for the treatment of postmenopausal estrogen deficiency symptoms. The applicant claims essential similarity to Livial (Organon Laboratories: PL 00065/0086) which has been licensed in the EU for more than 10 years and is currently licensed in the UK.

The drug is well established for use in the requested indication.

PLs 00530/0770-1 are duplicate applications of PL 00530/0708 and the applicant has confirmed that they have submitted copies of Modules 1 and 2 only and that modules 2,3, 4 and 5 supporting PL 00530/0770-71 are identical to those submitted with PL 00530/0708.

Good Clinical Practice (GCP) aspects

The single bioequivalence study supporting these applications was conducted according to GCP.

Orphan medicinal products

N/A

CLINICAL PHARMACOLOGY

Tibolone has the chemical formula $C_{21}H_{28}O_2$ i.e. $(7\infty,17\infty)$ -17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one.

The known pharmacokinetic (PK) and pharmacodynamic (PD) aspects have been reviewed in the Clinical Overview.

Pharmacokinetics

Introduction

Apart from a single bioequivalence study (Study P020214), no new PK studies have been performed.

Absorption

Bioequivalence (Study P020214)

The appropriate comparator, Livial (Organon), was used. This was an open-label, two-way, crossover, single-dose study designed to compare the oral bioavailability of the proposed product Tibolone (IVAX) with Livial. The study population consisted of healthy postmenpausal, female volunteers. There was an adequate, two-week, washout period between study arms. The protocol underwent appropriate ethical clearance and complied with GCP.

Pilot study

The main study was preceded by a pilot study designed to optimise the blood sampling schedule in the main study and to calculate definitive sample size based on power estimate. It was conducted in 6 healthy post-menopausal women using the same protocol and inclusion/exclusion criteria. PK parameters including C_{max} , T_{max} , $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$ were measured and as a result of the pilot, an additional blood sampling time point was added to improve the estimation of C_{max} and T_{max} .

Main study

26 healthy post-menopausal Caucasian women (FSH >40IU/L; estradiol <20pg.ml) aged 40-70 years were enrolled. The study medication (test product: 2.5mg Tibolone or reference product: Livial) was administered under fasting conditions. Blood samples for assay were collected immediately prior to dosing, then at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 then 24h post dosing.

Blood samples were taken for laboratory safety tests at screening and at the end of the study.

The geometric mean, SD and CV% for the PK parameters for Test and Reference product are shown in Table 1.

Table 1: Comparative PK parameters

N=26		C _{max}	T _{max} #	T _{lag} #	t _{1/2}	AUC _{0-t}	AUC _{0-∞}	F rel [#]
		pg/ml	h	h	h	h*pg/ml	h*pg/ml	
TEST	Geom	1377	0.5	0.00	5.59	2636	2963	0.92
Tibolone	Mean		[0.25-	[0.00-				[0.63-
	CV%		2.00]	0.00]				1.32]
		44			48	57	53	
REF	Geom	1373	1.00	0.00	5.24	2935	3293	-
Livial Mean			[0.50-	[0.00-				
CV%			2.50]	0.00]				
		51			43	45	44	-
Point Estimate		1.00	$NS^{(1)}$			0.90	0.90	
90% CI		[0.88-				[0.84-0.96]	[0.84-0.96]	
		1.15]						

#=median (min-max) value

(1)=Wilcoxon signed rank test

The study findings show that tibolone is rapidly absorbed from both formulations and maximum plasma concentrations (T_{max}) was achieved 0.25 - 2h post ingestion for the test

product cf. 0.5 - 2.5h for the reference product and no statistical difference in median T_{max} for the two products was found. Mean C_{max} was around 1375pg/ml for both.

Plasma concentrations declined bi-exponentially and the mean $T_{\frac{1}{2}}$ was comparable at 5.59h for the test, and 5.24h for the reference product.

Overall the mean AUC_{0-t} and $AUC_{0-\infty}$ were 10% lower for the test product, compared with the reference product. For $AUC_{0-\infty}$ the mean relative bioavailability (F rel) was 0.92 (range 0.63-1.32).

There was marked inter-individual variability in the measured PK parameters (C_{max} , $t_{1/2}$ and $AUC_{0-\infty}$), the CV% being between 43% and 53%, but this was similar for both the test and reference formulations. The estimation based on residual variability of the ANOVA was lower for C_{max} (29%) and $AUC_{0-\infty}$ (13%). No period or sequence effect was found. Intraindividual variation was found to be less marked.

From the data it can be concluded that the 90% CIs of the C_{max} , $AUC_{0-\infty}$ and AUC_{0-t} point estimates were within the 0.80-1.25 range (0.88-1.15; 0.84-0.96 and 0.84-0.96, respectively). The pre-specified CPMP criteria for bioequivalence, in terms of both rate and extent of absorption, were therefore satisfied in this study.

Safety findings are discussed under "Clinical Safety".

Assessor's comment

Bioequivalence has been adequately demonstrated. Although the mean $AUC_{0-\infty}$ and AUC_{0-t} were both 10% lower for the test product, the 90% CIs were nevertheless within the acceptance range and the small difference is therefore considered to be of no clinical relevance.

Distribution and elimination

No data are available on the distribution or elimination of tibolone itself (until recently there has been no available assay for unchanged tibolone). The $t_{1/2}$ of 14C-radiolabelled tibolone is around 45h. Protein-binding (albumin) is 96.3%. Tibolone and its metabolites have a low binding affinity for SHBG. Excretion is mainly via the faeces (60%), the rest is renal (40%). Entero-hepatic circulation does not occur.

Metabolism

Tibolone is known to be rapidly converted into three metabolites with different estrogenic and progestogenic properties: a $3\infty(OH)$ metabolite, a $3\beta(OH)$ metabolite and a 4-ene-isomer. This aspect is reviewed more fully in the Clinical Overview. Since cytochrome P450 is not involved in the major metabolic routes and tibolone and its metabolites are only weak inhibitors of cytochrome P450, clinically relevant interactions at the CYP450 level are not expected.

Pharmacokinetics of metabolites

No new studies have been conducted.

Intra- and inter-individual variability

This has been discussed above. The proposed product shows a similar degree of interindividual variability compared to Livial.

Special populations

No new studies have been performed.

The product is unsuitable for children.

Interactions

No new studies have been performed. The proposed Summary of Product Characteristics (SPC) contains the same information as that of the reference product, Livial.

Assessor's overall conclusions on pharmacokinetics

The current state of knowledge has been adequately reviewed by the applicant. Apart from a bioequivalence study to establish essential similarity, no new data are provided and none are required for this type of application. The bioequivalence study has established that both the rate and extent of absorption of the proposed formulation are equivalent to that of the reference product, Livial.

Pharmacodynamics

Introduction

Tibolone is a synthetic steroid which is structurally related to the progestogens norethynodrel and norethindrone, which are 19-nortestosterone derivatives. It has relatively weak estrogenic, progestogenic and androgenic properties; relative potencies being 1/10th that of estradiol, 1/8th that of norethisterone and 1/50th that of methyltestosterone.

Mechanism of action

A comprehensive literature review of both pre-clinical and clinical data is included in the Clinical Overview. The mechanism of action is complex and not fully understood.

Primary pharmacology

It is likely that the estrogenic or progestogenic properties vary depending upon the target tissue. Progestogenic effects predominate in the endometrium and there appears to be no estrogenic effect on breast, as shown by breast density measurements using mammography and low incidence of mastalgia. The effects on bone are probably via the estrogen receptor. Tibolone has an effect on endorphin levels and acts centrally to affect the thermoregulatory system – these two actions may account for the beneficial effects reported on mood and reduction in hot flushes/night sweats.

Secondary pharmacology

Unlike unopposed estrogen therapy, tibolone does not appear to cause endometrial hyperplasia/cancer. It is associated with a reversible effect on lipids: reduction in triglycerides

as well as VLDL and HDL (particularly apolipoprotein A1). LDL and total cholesterol are not affected. Compared with ethinylestradiol, tibolone is associated with lower levels of factor VII and VIII and higher levels of antithrombin III. It reduces serum fibrinogen, plasminogen-activator-antigen and plasminogen-activator-inhibitor-1 and increases plasminogen and antitrypsin-plasmin complex. There is no apparent effect on coagulation variables but this has not been fully evaluated. Tibolone stimulates fibrinolytic activity but appears to have no significant effect on haemostasis. A mild effect on glucose tolerance has been reported but fasting glucose and glycosylated proteins remain within the normal range. No clinically significant effects on BP or body weight have been reported.

Relationship between plasma concentration and effect

No new data are available. In humans, a daily dose of ≥ 2.5 mg suppresses FSH and LH levels and relieves postmenopausal symptoms. A daily dose of 1.25mg has inconsistent effects and doses of 5mg may be associated with vaginal bleeding.

Assessor's overall conclusions on pharmacodynamics

The current state of knowledge has been adequately reviewed by the applicant. No new data are provided and none are required for this type of application.

CLINICAL EFFICACY

Introduction

Tibolone formulations have been licensed for more than 10 years in the EU, including the UK, for the treatment of estrogen deficiency symptoms and as (now second-line) therapy for prevention of post-menopausal osteoporosis.

Dose-response studies and main clinical studies

No new studies have been performed and none are required for these applications.

Review of the literature

A full review of the literature on efficacy has been submitted in the Clinical Overview.

Vasomotor symptoms

Nine randomised trials (plus some non-randomised trials) have examined the effects of tibolone on vasomotor symptoms. Most of the studies compared tibolone with placebo but some compared it with conventional HRT. Tibolone has been shown to be superior to placebo with no evidence of tachyphylaxis.

The active comparator studies have generally shown that the effect of tibolone is quantitatively similar to conventional HRT (estrogen or estrogen+progestogen) and the absence of vaginal bleeding and low incidence of mastalgia with tibolone are welcomed by many patients.

Mood

This is a difficult parameter to assess and is linked to other menopausal symptoms including sleep disturbance/fatigue. The literature is conflicting but on balance there may be some beneficial effect.

Libido

This is a poorly understood area. The weak androgenic effect may theoretically improve libido but again the literature is conflicting although most studies show superiority relative to placebo, but not to estrogen alone, and some data appear to show superiority relative to the estrogen/norethisterone combination.

Other climacteric symptoms

Symptoms such as headache, insomnia, fatigue, dizziness and palpitations have been examined in some studies. There may be some evidence of a beneficial effect but there are conflicting findings.

Prevention of postmenopausal osteoporosis

The literature is reviewed in the Clinical Overview. Comparative studies have shown that tibolone is as efficacious as 2mg oral, $50\mu g/day$ of transdermal estradiol or standard doses of alendronate.

Assessor's overall conclusions on clinical efficacy

Provided, as is the case, essential similarity based on bioequivalence to Livial is demonstrated, efficacy for the licensed indications for Livial is assumed and no new efficacy data are required. Since the applications were submitted, a safety restriction has been put into place. As a result, tibolone (and conventional HRT) may now only be licensed as 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'.

CLINICAL SAFETY

Introduction

Concerns regarding the safety of conventional HRT have been highlighted by the early termination of part of the Women's Health Initiative (WHI) trial which showed a small, but increased, risk of developing breast cancer, cardiovascular disease, stroke and thrombotic events with one particular type of HRT combination.

Apart from the limited safety data derived from the bioequivalence study discussed above, no new clinical safety data have been submitted with this application and none are required as the same safety profile as Livial can be assumed.

Study P020214

Patient exposure

26 subjects received both Tibolone (IVAX) and Livial and all received a total of 5.0mg of tibolone (2.5mg in each treatment arm).

Adverse events

No serious adverse events (AEs) were reported. A total of 7 AEs were reported in six subjects and all were either mild or moderate in severity. Of these, 4 AEs were reported while taking the test product (Tibolone, IVAX): 3 headaches and one episode of vomiting - considered possibly or probably related to treatment. In subjects taking the reference product, Livial, three AEs were reported: an episode of hot flushes, one episode of rhinitis and one headache. The hot flushes and headache were considered possibly related to study medication but the rhinitis was considered unlikely to be related. Only one AE required treatment i.e. paracetamol for headache.

Literature review

The literature has been reviewed in the Clinical Overview. No new findings have been reported which would impact on the SPC wording for Livial to which the proposed wording for Tibolone (IVAX) should be consistent. The commonest reported adverse effects associated with tibolone therapy are weight gain, acneform rash, seborrhoeic dermatitis, dizziness, headache, gastrointestinal symptoms, increased facial hair and pretibial oedema. However, the frequency is comparable to that on placebo.

The incidence of breakthrough bleeding on tibolone taken within the first year of the menopause is about 20%. Patients who have detectable levels of estrogen and who are younger/recently menopausal are the group most likely to bleed. The incidence in older women was found to be about 7% in one study.

Endometrial hyperplasia is not associated with tibolone treatment; the endometrium is unchanged or becomes atrophic. One study involving 85 women who presented with postmenopausal bleeding while on tibolone revealed the presence of endometrial polyps in 72%. It is unclear whether there is a causal link with tibolone therapy.

In light of the WHI and Million Women Studies, a major concern regarding long-term use of HRT is the potential association with carcinoma of the breast. It is well known that conventional HRT with estrogen, alone or in combination with a progestogen, changes the density of breast tissue on mammography which may be associated with subsequent malignancy. Tibolone has been shown to have tissue selectivity and with its metabolites will reduce the estrogen level in breast tissue mainly by inhibition of sulphatase activity (which transforms estrone sulphate to estrone). Clinical studies support the hypothesis that tibolone is less stimulatory to breast tissue than conventional HRT. There is currently controversy about the use of tibolone in patients who have had carcinoma of the breast and in the Livial SPC the use of tibolone is, at the moment, contraindicated in the presence of any hormone-dependent tumour. An international multicentre randomised trial known as the LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) study, is designed to investigate the possible benefits of tibolone (Livial) in women with a history of breast cancer who are experiencing menopausal symptoms. The aim is to recruit

2,600 women and to look at breast cancer recurrence and Quality of Life (QoL) over a minimum 5 year period. The findings will be of great interest.

Post marketing experience

There are no new data to impact on the established SPC wording for the reference product, Livial, with which the proposed product should be consistent.

Assessor's overall conclusions on clinical safety

The wording in the proposed SPC is consistent with the experience to date with tibolone, the SPC for the reference product Livial and takes into account the latest safety wordings for the core HRT text based on the WHI/MWS study findings.

CLINICAL EXPERT

A qualified Clinical Expert is named.

SPC/PIL AND LABEL

Satisfactory.

OVERALL RISK-BENEFIT ASSESSMENT

The efficacy of tibolone in the treatment of postmenopausal symptoms is established and these products which, on the basis of bioequivalence, have been demonstrated to be essentially similar to the innovator reference product Livial, would be expected to have equivalent efficacy in the approved indications. There are no recent safety concerns apart from those arising from the WHI/MWS which are already incorporated into the Livial SPC and have been duly included in the proposed Tibolone (IVAX) SPCs.

Marketing authorisations may, therefore, be granted.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Tibolone 2.5mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Tibolone 2.5mg Tablets and Livial 2.5mg Tablets (PL 00065/0086).

No new or unexpected safety concerns arise from this application.

The SPCs, PILs and labelling are satisfactory and consistent with that for Livial 2.5mg Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the innovator product are interchangeable. The efficacy of tibolone in the treatment of postmenopausal symptoms is established. The risk-benefit assessment is therefore considered to be favourable.

PL 00530/0708

STEPS TAKEN FOR ASSESSMENT

2.5mg Tablets on 27 November 2003. The MHRA's assessment of the submitted quality data was completed on 30 April 2004. Further information (quality) was requested from the company on 30 April 2004. The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.	1	The MHRA received the marketing authorisation application for Tibolone
The MHRA's assessment of the submitted quality data was completed on 30 April 2004. Further information (quality) was requested from the company on 30 April 2004. The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.	1	•
April 2004. Further information (quality) was requested from the company on 30 April 2004. The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.		
Further information (quality) was requested from the company on 30 April 2004. The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.	2	The MHRA's assessment of the submitted quality data was completed on 30
2004. The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.		April 2004.
The MHRA's assessment of the submitted clinical data was completed on 9 August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.	3	Further information (quality) was requested from the company on 30 April
August 2004. Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.		2004.
 Further information (clinical) was requested from the company on 10 August 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006. 	4	The MHRA's assessment of the submitted clinical data was completed on 9
 2004. The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006. 		August 2004.
 The applicant's responses to further information request (quality) were received on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006. 	5	Further information (clinical) was requested from the company on 10 August
on 1 October 2004 and 22 October 2004. The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.		2004.
 The applicant's response to further information request (clinical) was received on 26 October 2004. Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006. 	6	The applicant's responses to further information request (quality) were received
on 26 October 2004. 8 Additional information (quality) was requested from the company on 2 February 2005. 9 The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. 10 The MHRA completed its assessment of the application on 10 April 2006.		on 1 October 2004 and 22 October 2004.
Additional information (quality) was requested from the company on 2 February 2005. The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.	7	The applicant's response to further information request (clinical) was received
2005. 9 The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. 10 The MHRA completed its assessment of the application on 10 April 2006.		on 26 October 2004.
9 The applicant responded to additional information request (quality) in letters dated 19 July 2005, 22 December 2005 and 11 January 2006. 10 The MHRA completed its assessment of the application on 10 April 2006.	8	Additional information (quality) was requested from the company on 2 February
dated 19 July 2005, 22 December 2005 and 11 January 2006. The MHRA completed its assessment of the application on 10 April 2006.		2005.
The MHRA completed its assessment of the application on 10 April 2006.	9	The applicant responded to additional information request (quality) in letters
		dated 19 July 2005, 22 December 2005 and 11 January 2006.
	10	The MHRA completed its assessment of the application on 10 April 2006.
11 The application was determined on 10 April 2006.		
	11	The application was determined on 10 April 2006.

TIBOLONE 2.5MG TABLETS

PL 00530/0770 PL 00530/0771

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received marketing authorisation applications for Tibolone 2.5mg
	Tablets on 16 May 2005. It was requested that these applications be assessed in
	parallel with PL 00530/0708.
2	Further information (quality) was requested from the company on 14 December
	2005.
3	The applicant responded to further information request (quality) in a letter dated
	11 January 2006.
4	Further information (clinical) was requested from the company on 27 March
	2006.
5	The applicant's response to further information request (clinical) was received
	on 10 April 2006.
6	The MHRA completed its assessment of the applications on 10 April 2006.
7	The applications were determined on 10 April 2006.

PL 00530/0708 PL 00530/0770 PL 00530/0771

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
Subiliteed	сурс		

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tibolone 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of tibolone For excipients, see 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 the menopause.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures when other treatments for this indication are considered unsuitable (e.g. in the case of intolerance or contraindications).

4.2. Posology and method of administration

For Oral use

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.

Starting Tibolone

For the treatment of vasomotor symptoms and the prevention of osteoporosis -

- 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
- Women being treated with gonadotrophin releasing hormone (GnRH) analogues, for example, for endometriosis, 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

Hypersensitivity to the active ingredient or any of the constituents of the product. Pregnancy or lactation.

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).

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction). 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine

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.

In women with an intact uterus, the risks of breast cancer and endometrial cancer (see below and section 4.8) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers, in terms of their response to treatment, morbidity and mortality.

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

Endometrial hyperplasia and cancer

- 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 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 non-randomised, observational, 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 observational 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.

Venous thromboembolism

- Estrogen or estrogen-progestogen 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.

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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- 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 postmenopausal women or other HRT products, or tibolone.

4.5. Interactions with other medicinal products and other forms of interaction

No examples of interactions between tibolone and other medicines have been reported in clinical practice. 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 decrease its therapeutic effect.

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.

4.6. Pregnancy and lactation

Tibolone is contraindicated during pregnancy and lactation (see section 4.3). 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.

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

Occasionally, vaginal bleeding or spotting may occur, mainly during the first months of treatment. Other adverse events that have been observed occasionally include: Dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, oedema, and effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

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.

Table 1 Undesirable effects of Tibolone

System organ class	Common >1%,<10%	Uncommon >0.1%,<1%
Gastrointestinal disorders	Abdominal pain	
Metabolicand nutritional disorders	Weight Increase	
Reproductive disorders, female	Vaginal bleeding or spotting Leukorrhoea Breast pain Genital pruritus Genital monoliasis Vaginitis	
Skin and appendages disorders	Hypertrichosis	
Central and peripheral nervous system disorders		Amnesia

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 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 year's use
- between 18 and 20 (best estimate =19) for 10 years' use

For women who take tibolone, the number of extra cases of breast cancer are expected to be about the same as for estrogen-only HRT.

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

This 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 Section 4.3 Contraindications and 4.4 Special warnings and precautions for use;
- Myocardial infarction and stroke;
- Gall bladder disease:
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
- Probable dementia (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

ATC Code: GO3D-C05 Urogenital system (including sex hormones)

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 ($\Delta 4$ -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 $\Delta 4$ -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
- In the endometrium, tibolone and its estrogenic 3β -OH metabolite are converted to the progestogenic/androgenic $\Delta 4$ -isomer. In addition, the $\Delta 4$ -isomer cannot be reduced by the 5α -reductase enzyme to a less active progestogen. This considerably prolongs the presence of the $\Delta 4$ -isomer and thus the progestogenic activity in the endometrium.

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

- The incidence of vaginal bleeding is no higher than that with placebo use. In women in whom some endogenous estrogen is still produced, vaginal bleeding may occur during tibolone therapy because of an apparently stimulated endometrium.
- 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

In vitro data indicate that, in the breast, tibolone inhibits the sulfatase enzyme thereby reducing the levels of active estrogens in this tissue.

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 $\Delta 4$ -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 -OH metabolites are higher but accumulation does not occur.

Table 2: Pharmacokinetic parameters of Tibolone

	•		3α-	OH	3β-0	Н		
	tib	olone	meta	bolite	metab	olite	$\Delta 4$ -iso	omer
	$\overline{\text{SD}}$	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 consumption of food has no significant effect on the extent of absorption

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. Although a carcinogenic effect 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

Starch Pregelatinized Ascorbyl Palmitate (E304) Tri sodium Citrate Dihydrate Sodium Lauryl Sulphate Croscarmellose Sodium Magnesium Stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions. Keep blister in the outer carton

6.5. Nature and contents of container

PVC-PVdC /aluminium foil blisters in pack sizes of 28, 30, 60, 84 and 100 tablets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not Applicable.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd (trading as IVAX Pharmaceuticals UK) Albert Basin, Royal Docks London, E16 2QJ United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00530/0708

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2006

10 DATE OF REVISION OF THE TEXT

10/04/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tibolone 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of tibolone For excipients, see 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 the menopause.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures when other treatments for this indication are considered unsuitable (e.g. in the case of intolerance or contraindications).

4.2. Posology and method of administration

For Oral use

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.

Starting Tibolone

For the treatment of vasomotor symptoms and the prevention of osteoporosis -

- 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
- Women being treated with gonadotrophin releasing hormone (GnRH) analogues, for example, for endometriosis, 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

Hypersensitivity to the active ingredient or any of the constituents of the product. Pregnancy or lactation.

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).

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine

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.

In women with an intact uterus, the risks of breast cancer and endometrial cancer (see below and section 4.8) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers, in terms of their response to treatment, morbidity and mortality.

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

Endometrial hyperplasia and cancer

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 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 non-randomised, observational, 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 observational 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.

Venous thromboembolism

- Estrogen or estrogen-progestogen 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.

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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- 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 postmenopausal women or other HRT products, or tibolone.

4.5. Interactions with other medicinal products and other forms of interaction

No examples of interactions between tibolone and other medicines have been reported in clinical practice. 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 decrease its therapeutic effect.

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.

4.6. Pregnancy and lactation

Tibolone is contraindicated during pregnancy and lactation (see section 4.3). 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.

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

Occasionally, vaginal bleeding or spotting may occur, mainly during the first months of treatment. Other adverse events that have been observed occasionally include: Dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, oedema, and effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

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.

<u>Table 1 Undesirable effects of Tibolone</u>

System organ class	Common >1%,<10%	Uncommon >0.1%,<1%
Gastrointestinal disorders	Abdominal pain	
Metabolicand nutritional disorders	Weight Increase	
Reproductive disorders, female	Vaginal bleeding or spotting Leukorrhoea Breast pain Genital pruritus Genital monoliasis Vaginitis	
Skin and appendages disorders	Hypertrichosis	
Central and peripheral nervous system disorders		Amnesia

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.

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 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 year's use
- between 18 and 20 (best estimate =19) for 10 years' use

For women who take tibolone, the number of extra cases of breast cancer are expected to be about the same as for estrogen-only HRT.

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

This 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 Section 4.3 Contraindications and 4.4 Special warnings and precautions for use;
- Myocardial infarction and stroke;
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
- Probable dementia (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

ATC Code: GO3D-C05 Urogenital system (including sex hormones)

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 ($\Delta 4$ -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 $\Delta 4$ -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
- In the endometrium, tibolone and its estrogenic 3β -OH metabolite are converted to the progestogenic/androgenic $\Delta 4$ -isomer. In addition, the $\Delta 4$ -isomer cannot be reduced by the 5α -reductase enzyme to a less active progestogen. This considerably prolongs the presence of the $\Delta 4$ -isomer and thus the progestogenic activity in the endometrium.

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

- The incidence of vaginal bleeding is no higher than that with placebo use. In women in whom some endogenous oestrogen is still produced, vaginal bleeding may occur during tibolone therapy because of an apparently stimulated endometrium.
- 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

In vitro data indicate that, in the breast, tibolone inhibits the sulfatase enzyme thereby reducing the levels of active estrogens in this tissue.

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 $\Delta 4$ -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 -OH metabolites are higher but accumulation does not occur.

Table 2: Pharmacokinetic parameters of Tibolone

	-		3α-0	ОН	3β-0	Н		
	tib	olone	meta	bolite	metab	olite	$\Delta 4$ -iso	omer
	$\overline{\text{SD}}$	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 consumption of food has no significant effect on the extent of absorption

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. Although a carcinogenic effect 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 Starch Pregelatinized Ascorbyl Palmitate (E304) Tri sodium Citrate Dihydrate Sodium Lauryl Sulphate Croscarmellose Sodium Magnesium Stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions. Keep blister in the outer carton

6.5. Nature and contents of container

PVC-PVdC /aluminium foil blisters in pack sizes of 28, 30, 60, 84 and 100 tablets. Not all pack sizes may be marketed.

6.7 Instructions for use and handling

Not Applicable.

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd (trading as IVAX Pharmaceuticals UK) Albert Basin, Royal Docks London, E16 2QJ United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00530/0770

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2006

10 DATE OF REVISION OF THE TEXT

10/04/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tibolone 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of tibolone For excipients, see 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 vear after the menopause.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures when other treatments for this indication are considered unsuitable (e.g. in the case of intolerance or contraindications).

4.2. Posology and method of administration

For Oral use

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.

Starting Tibolone

For the treatment of vasomotor symptoms and the prevention of osteoporosis -

- 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
- Women being treated with gonadotrophin releasing hormone (GnRH) analogues, for example, for endometriosis, 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

Hypersensitivity to the active ingredient or any of the constituents of the product. Pregnancy or lactation.

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).

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactase malabsorption should not take this medicine

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.

In women with an intact uterus, the risks of breast cancer and endometrial cancer (see below and section 4.8) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers, in terms of their response to treatment, morbidity and mortality.

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

Endometrial hyperplasia and cancer

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 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 non-randomised, observational, 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 observational 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.

Venous thromboembolism

- Estrogen or estrogen-progestogen 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.

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.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- 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 postmenopausal women or other HRT products, or tibolone.

4.5. Interactions with other medicinal products and other forms of interaction

No examples of interactions between tibolone and other medicines have been reported in clinical practice. 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 decrease its therapeutic effect.

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.

4.6. Pregnancy and lactation

Tibolone is contraindicated during pregnancy and lactation (see section 4.3). 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.

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

Occasionally, vaginal bleeding or spotting may occur, mainly during the first months of treatment. Other adverse events that have been observed occasionally include: Dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, oedema, and effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

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.

<u>Table 1 Undesirable effects of Tibolone</u>

System organ class	Common >1%,<10%	Uncommon >0.1%,<1%
Gastrointestinal disorders	Abdominal pain	
Metabolicand nutritional disorders	Weight Increase	
Reproductive disorders, female	Vaginal bleeding or spotting Leukorrhoea Breast pain Genital pruritus Genital monoliasis Vaginitis	
Skin and appendages disorders	Hypertrichosis	
Central and peripheral nervous system disorders		Amnesia

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.

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 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 year's use
- between 18 and 20 (best estimate =19) for 10 years' use

For women who take tibolone, the number of extra cases of breast cancer are expected to be about the same as for estrogen-only HRT.

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

This 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 Section 4.3 Contraindications and 4.4 Special warnings and precautions for use;
- Myocardial infarction and stroke;
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
- Probable dementia (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

ATC Code: GO3D-C05 Urogenital system (including sex hormones)

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 ($\Delta 4$ -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 $\Delta 4$ -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
- In the endometrium, tibolone and its estrogenic 3β -OH metabolite are converted to the progestogenic/androgenic $\Delta 4$ -isomer. In addition, the $\Delta 4$ -isomer cannot be reduced by the 5α -reductase enzyme to a less active progestogen. This considerably prolongs the presence of the $\Delta 4$ -isomer and thus the progestogenic activity in the endometrium.

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

- The incidence of vaginal bleeding is no higher than that with placebo use. In women in whom some endogenous oestrogen is still produced, vaginal bleeding may occur during tibolone therapy because of an apparently stimulated endometrium.
- 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

In vitro data indicate that, in the breast, tibolone inhibits the sulfatase enzyme thereby reducing the levels of active estrogens in this tissue.

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 $\Delta 4$ -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 -OH metabolites are higher but accumulation does not occur.

Table 2: Pharmacokinetic parameters of Tibolone

	•		3α-	OH	3β-0	Н		
	tib	olone	meta	bolite	metab	olite	$\Delta 4$ -iso	mer
	$\overline{\text{SD}}$	MD	SD	MD	SD	MD	SD	<u>MD</u>
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 consumption of food has no significant effect on the extent of absorption

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. Although a carcinogenic effect 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 Starch Pregelatinized Ascorbyl Palmitate (E304) Tri sodium Citrate Dihydrate Sodium Lauryl Sulphate Croscarmellose Sodium Magnesium Stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions. Keep blister in the outer carton

6.5. Nature and contents of container

PVC-PVdC /aluminium foil blisters in pack sizes of 28, 30, 60, 84 and 100 tablets. Not all pack sizes may be marketed.

6.8 Instructions for use and handling

Not Applicable.

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd (trading as IVAX Pharmaceuticals UK) Albert Basin, Royal Docks London, E16 2QJ United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00530/0771

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2006

10 DATE OF REVISION OF THE TEXT

10/04/2006

Patient Information Leaflets

PL 00530/0708

X

ibolone 2.5mg Tablets

Please read this leaflet carefully before you start to take your tablets.

It contains important information.

Sure about anything, or you want to know more, ask your Tablets on those side of the side doctor or a pharmacist.

Keep this leaflet safe, as you may want to read it again.

About your tablets

Your tablets are called Tibolone 2.5mg Tablets. They are part of a group of drugs called hormone replacement therapy (HRT).

What is in your tablets

What is IN YOUR GODESS
Each tablet contains

Thombor 2.5mg (active ingredent) and

Luctose Monthjolder, Starch Pregulatimed,
Ascotyl Palmittee (Edod, Tit sodium Citrate
Orlysider, Sodium Lany) (Splytes)
(other ingredents).

Tableta: 2.5mg (active ingredents).

Tableta: 3.5mg (active ingredents).

Tableta:

If you are not Who makes your tablets

What your tablets do

Thickne belong to a group of medicines called
homone reglacement therapy (HST).
Thickne is slightly different to most HST instead
of actual homoness (such as estrogen and
homoses (such as estrogen and
homoses) (such as estrogen
and progregates) (such as estrogen
homoses) (such as estrogen
homoses)

Before you take your tablets

tablets
Vou should need this exciton carefully, as well as benefits, 18th Dax some ricks that you need to consider when you are deciding whether to use it, or whether to care, or whether to care you usually to some women should not use Titolane you stable if you. He was not to take your shallest if you. He was not to take your shallest if you. He was not not to take your shallest if you. He was not have but, another type of cancer (particularly one which it is homome dependent) as although care to the whole you which is homome dependent, as the your which is homome dependent, as the your which is homome dependent, as they will be the your which is homome dependent.

- as blood clots in the veins of the legs or in the lungs.

 Have ever had a heart condition such as angina or a heart attack.

- tiese wer had a heart condition such as angina or a heart station.

 are pregnant, may become pregnant or are breast-dealing.

 have ever had a bad reaction to Tibolone or any of the taggedents lated in the What is in your of the taggedents lated in the What is in your of the you staffer from a hereditary condition called perphysia.

 If you have an intolerance to Luctone if you saffer from sucusal vaginal bleeding oil you saffer from some later disease. If the answer to any of these to you affer from some later disease of the across to any of these is you affer from the later to a saffer you?

 If you did not not the later that or an effect with the contract of the property of the saffer of the s

What I need to know before taking my medicine

rou around not tase? Now on the charge of th

If you are changing over from another type of HIT where you have a princip data taking 'Telone the younge's princip over from a period free HIT you are changing over from a period free HIT you can also start taking it movil you are being you and not set straight away. You are being you are consistent taking it was not been you will you have, or have even had, any of the following conditions, you if you have, or have even had, any of the following conditions. Best Bood dots: 8 Red these who have had blood clots Chose relatives funders, sitter, grandmother) with his had breset cance to their distance when the princip sitter, grandmother with the situation of the princip sitter of the princip to their distance when the princip will be the distance with the princip William of the princip William

- who has had breast cancer
 High blood pressure
 Uher disease
 High cholesterol levels
 Kidney disease
 Diabetes
 Galittones
 A rare disease called systemic lupus
 erythernatoous

- erytness. Eplepsy Asthma
- Ashma
 Migraine
 Otosclerosis (a hearing disorder)
 If any of the above apply to you:
 Have you to by our doctor? If not, talk to the doctor as soon as you can before taking Tibolone tablets. He or she may want to do some tests, or give you more advice about taking Tibolone.

Safety of HRT

Safety of HRT

As well as benefit, HRT has some rick which you take it, or whether to carry on taking. It will be take it, or whether to carry on taking. It helded check-ups below you start taking HRT, your doctor should ade below you start taking HRT, your doctor should ade below you start taking HRT, your doctor should ade to be the start taking HRT, your doctor should ade to be read to the simple your doctor may dockle to acmine your lessest your doctor may dockle to acmine your less and on the same and you will be a seen as the same and the

recently. If you have ever had heart disease, talkt your doctor to see if you should be taking left. Hert Will not help to prevent heart disease, Studies with one type of Int'll Containing compagated entogen flow the propercione IMPA, or conjugated entogen flow the propercione IMPA, the conjugated entogen flow the three Impacts in the conjugate Impacts in the Impacts

- If you're off your feet for a long time because of major surgey, hjuries or finess
 If you have a rare condition called systemic lupus erythematous (SLE)
 If any of these things apply to you, talk to your doctor to see if you should take HRT.

In any of these trangs apply to you, can to your and you from the transparence of the compare of

Effects on your risk of Alexaloping cancer Breast Cancer.

Women who have breast cancer, or have had or tibolone.

Taking HRT alightly increases the risk of breast risk of the risk of

of 65. For women who start taking estrogen-only HRT at age 50 and take it for 5 years, the figure will be between 33 and 34 in 1000 (i.e., an extra 1-2

cases). If they take estrogen-only HRT for 10 years, the

For women who start taking estrogen plus progestogen HRT at age 50 and take it for 5 years, the figure will be 38 in 1000 (i.e. an extra 6 cases).

is cases). The figure will be \$1 in 1000 (i.e. an extra flyounce) the figure will be \$1 in 1000 (i.e. an extra flyounce) the figure will be \$1 in 1000 (i.e. an extra flyounce) the standards in your breast, such as display of the stan changes in the nigole of any lumps you can see or feel our doctor as Habba an appointment to see your doctor as Habba and spointment to see your doctor as the standards and t

womanium sumer (cancer of the lithing of the woman is many more only left for a long time can cannot be supported by the first of the lithing of the count of the lithing of the count (in the lithing of the count of the summarium). Taking a repostagen as well as the estrogen left to lower the extra nit. You suitli have your womb, you doctor may prescribe a properticed spanned; or as a country of the country o

hysterectoraly, Your doctor will discuss with you whether your can asily take estigate without if you've had your worsh removed because of endometriosis, any endometrium left your body may be at risk. So your doctor may prescribe HET, which was not the properties of your properties of the properties

medicine.

If you get a breakthrough bleeding or spotting, it is usually nothing to worny about, especially during the first few months of taking HRT.

But if the bleeding or spotting.

carries on for more than the first few months

thicner.

Ovarian cancer

Ovarian cancer (cancer of the ovaries) is very rare,

but it is serious. It can be difficult to diagnose because there are often no obloos signs of the disease. See here who detailed that diagnose come studies of the diagnose of

Taking other medicines

Taking Other medicines
Tellyour doctor or phirmacist if you are taking, have recently taken, or intend to take any other doctors are consistent or taken and the control of the periodicine in the periodicine in the periodicine in the periodicine in the control of the periodic in t

- eg, warfarin/anticoagulunyout tablets
 insulin or other drugs used to treat diabetes

How to take your tablet

It is important to take your tablets only as directed. The important of table is to tablet every day. The important of tablet is to tablet every day. This important is tablet every day in the important is tablet in the important in the importan

What to do if you take too many tablets

It is important not to take too many tablets. Contact your nearest hospital casualty department or a doctor for advice if you have swallowed too many tablets or if you think a child has swallowed

any.

Symptoms may include nausea, vomiting and vaginal bleeding in women and young girls. Take this leaflet, and any tablets that you still have to show the doctor. Possible side effects

Please also see the section Safety of HRT in this leaflet.

You may have some side effects while you are taking your tablets these being controlled the property of the pr

- treatment

 Sudden disturbances to your vision

 Tell your pharmacist or doctor if you notice any
 other side-effects from your medicine, which are
 not mentioned here.

Looking after your tablets Keep your tablets in a safe place where children cannot see or reach them. Do not tale the tablets after the 'use by' date printed on the labels/catro. Keep your tablets in the pack they came in. Keep tikes in the pack they came in. This medicinal product does not require any special

PL number 0530/0708

This leaflet was written in March 2006

Tibolone 2.5mg Tablets

PL 00530/0770

Tibolone 2.5mg Tablets

Please read carefully before you start to take your tablets.

It contains important information.

you want to know more, What your tablets do Titokne belongs to a group of medicines called ask your doctor or a pharmacist.

Keep this leaflet safe, as you may want to read it again.

About your tablets

Your tablets are called Tibolone 2.5mg Tablets. They are part of a group of drugs called hormone replacement therapy (HRT).

What is in your tablets

- Enh tablet contains

 Thobne 25mg (atthe lage-derit) and

 Thobne 25mg (atthe lage-derit) and

 Lactone Monophant, Starch Pregelatinized,
 Accopity Palmitate (250d). It sockan Citrate

 Contamination Social Palmitate (250d) and Starch

 Contamination Social Palmitate Instead

 (other lage-derit). Thobase 25mg Application

 Tablets 25mg Application are out of white, flat

 Tablets 25mg Application are out of white, flat

 Tablets 25mg Application are out of white, flat

 Tablets 25mg Application are out of white and

 25° on the reverse.

 Tablets 25mg Application are out of the pack design of 28, 30, 60, 64 and 100 tablets. Not all pack deep

 of 28, 30, 60, 64 and 100 tablets. Not all pack deep

 or marketed.

If you are not Who makes your tablets

Sure about

The marketing authorisation holder and manufacturer is NAX Pharmaceuticals, Albert Bash, Royal Docks, London E16 2QJ.

Before you take your tablets

Vou should need this section carefully. As well as benefits, HET has some rids that you need to consider when you are deciding whether to care journey or the properties of th

- The enter many at those constituted discorder Such large.

 I have ever had a heart condition such as angina or a heart state,

 a repreparet, may become pregnant or are preparet, may become pregnant or any of the preparet such as any of the preparet state or the control of the such as a proper state or any of the preparet state or the What is in your staket's section.

 I you have an intellegence to Luctoce or any of the preparet state of the what is in your staket's section and hereafting confliction called prophysis.

 If you saffer from ususual variety and bleeding of you saffer from ususual variety and the state of the s

before taking my medicine

Tibolone will not protect you from pregnancy. You should not take Tibolone until at least 12 months after your last natural menstrual bleed

Thomas Security to the table by fulfillers flyou have had your worth and coaties removed growth or the security of the security of the growthought releasing floormone (coller) enablepast, for conditions such as endometrious growthought releasing floormone (coller) are the security of the security of the you have never used HRT before, you can start taking Todone straight away. You are changing over from another type of HRT - there are several different types of HRT, such exclusions are second and the progression with some you have a period, and with some you don't gest-differ helfs."

If you are changing over from another type of HET where you have a period, start taking Tbelone soon as you probled with an a particle fit if you are changing over fit straight energy. You can also start straight energy. You can also start straight energy. You can also start straight energy if you are being treated for endometricus. Your doctor may need to keep a close work not you if you have, or have ever had, any of the following conditions.

- ollowing conditions:
 Uterline (round) bithorids
 Blood clots
 Blood clots
 Blood clots
 Close relatives (mother, sister, grandmother)
 High blood pressure
 Liber disease
 Liber disease
 Blood pressure
 Liber disease
 Blood pressure
 Blood pre

Safety of HRT

Safety of HRT

As well as benefits, HRT has some rids which you need to conside when you are desding whether to meed to conside when you are desding whether to meed to conside when you have the property of the property of

smear tests

Regularly check your breasts for any changes such as dropping of the sixt, changes in the nipping of or any tumps you can see or feel.

Effects on your heart neciculation Heart disease HRT is not recommended for women who have heart disease, or have had heart disease.

risk is leasy to be similar, attough this is not yet fightings?

a pain in your chest that spreads to your am or next. See a doctor as soon as possible and do soon and the soon as possible and do you can. This pain could be a sign of heart disease, stroke Becent research auguests that HET slightly research the size of brings a strike. One things remarks the first of harder is challed getting older in the first of stroke include: getting older smalled smalled to much alcohol driving too much alcohol if you are wornied about any of these things, or fly you have had a stroke in the past, talk to your doctor to seelf you should take HIT. Looking at women in their 50x who are not

dictor to see if you should tale HIXT.

Compare

Looking are in their 500 who are not

Looking are in their 500 who are not

Looking are looking on a 5-year period, 3 in

1000 would be expected to have a study.

For women in their 500 who are taking HIXT, the

figure would be 4 in 1000 Go. who are not

Looking at women in their one of 5-year period, 11

In 1000 would be expected to have a study.

For women in their 600 who are taking HIXT, the

figure would be 1 in 1000.

Light Signer would be 1 in 1000.

Looking at women in their Signer would be 1 in 1000.

Looking at women in 10000.

Looking at women in 1000.

Looking at women in 10000.

Looking at women in 100000.

Looking at women in 1000

blood Clots
Blood

- venous thromboembolism, or VTE.
 You are more lifely to get a blood dot:

 If you are sentually overveight

 If you have had a blood dot before

 If any of you close famly have had blood dots

 If you have had one or more miscarriages

 If you have had one or more miscarriages

 If you have any blood dotting problem that
 needs treatment with a medicine such as
 weed fails.

- If you're off your feet for a long time because of major surgery, injuries or liness
 If you have a rare condition called systemic lupus erythematosus (SLE)
 If any of these things apply to you, talk to your doctor to see if you should take HRT

- If any of these things apply to you, talk to your doctor to see if you should tale HIT doctor to see if you should tale HIT doctor to see if you should tale HIT doctor to you should tale HIT doctor to you should tale with the total part of the the total part of th

- Women on the past, SHOWN or tholone. Taking HRT slightly increases the risk of breast cancer; so does having a later menopause. The risk cancer; so does having a later menopause after a cancer; so does having a later men

- of 65.

 For women who start taking estrogen-only HRT at age 50 and take it for 5 years, the figure will be between 33 and 34 in 1000 (i.e. an extra 1-2
- cases), If they take estrogen-only HRT for 10 years, the

- years, the figure will be 3 to 1,000 (b. a. an extra of cases).

 If they tale entrogen plus progestogen HRT for 10 to cases), and they tale entrogen will be 3 to 1,000 (b., an extra 10 cases), and they can be set of cases of the set of cases of the set of the set
- whether you can safely take estrogen without projectiogar. your work remove because of endometriosis, any endometrian left in your box endometriosis, any endometrian preparise left that includes a projectogen as well as an estrogen because Tholore is slightly different from moz. HIT (see the section "What your tablets do'l) you don't need to take a separate projectogen when you are taking Tholore. Compare
- you are stang thooses. Looking at women who still have a uterus who are not taking HRT on average 5 in 1000 will be diagnosed with endomental cancer between the For women who take extractly a standard control of the form who will be stronger only HRT, the ranker will be 2 to 12 times highly-depending on the dose and how long you take it. The addituse of preparingent to settlementally the highly of the standard control of the standar
- me womb increases the longer you take the medicine.

 In the control of the contro
- Ovarian cancer
 Ovarian cancer (cancer of the ovaries) is very rare,

- but it is serious. It can be difficult to diagnose, because there are often no obvious signs of the
- Some studies have indictated that taking estrogen-only HRT for more than 5 years may increase the risk of ovarian cancer. It is not yet known whether other kinds of HRT increase the risk in the same way.
- way.

 <u>Dementia</u>
 HRT will not prevent memory loss. In one study of women who started using combined HRT after the age of 65, a small increase in the risk of dementia was observed.

Taking other medicines

- Taking Other medicines

 Fellyour doctor pharmacist flyou are taking, have recently taken, or intend to take any other medicines, including flowe you may have bought medicines. Including flowe you may have bought important if the other medicine is.

 Feldorise used to test epilepsy (filty such as babilitatives, carbanisaspine or phraython infection such as filtrappics.

 Feldorise used in the state of test infection such as filtrappics.

 Feldorise used to treat flood close (thrombost) e.g. warfaring articogalant/blood throught.

How to take your tablet

- It is important to take your tablets only as directed by the doctors or harmacist. The recommended dose to not tablet every day. The recommended dose to not tablet every day. The recommended without chaving with some water. Table your tablet at the same time every day. Use in Children-Children doud not our Thoone. If you frage to table a tablet table it as soon as you remove the miles you are more than 12 hours false. If you're late by more than 12 hours just slip the mixed tablet.

What to do if you take too many tablets

- any.

 Symptoms may include nausea, vomiting and vaginal bleeding in women and young girls. Take this leaflet, and any tablets that you still have to show the doctor.

Possible side effects

Please also see the section Safety of HRT in this

joints. Stop taking the tablets and one stop taking the tablets and one some stop taking of the stop taking tablets and tablet data (but the following like), and a labod data (but the following like), and the stop tablets of the stop tablets of the stop tablets of the stop tablets of t

- fromediates:
 Symptoms to book out for:
 Symptoms to book out for:
 Symptoms to book out for:
 Symptoms to murbones in an arm or leg
 Sudden discolouration of your alkn
 Sudden discolouration of your alkn
 Sudden shortness in your chest
 Sudden shortness of breath
 Sudden shortness of breath
 Other so of fairting
 Sudden shortness of breath
 Sudden shortn treatment
 Sudden disturbances to your vision
 Tell your pharmacist or doctor if you notice any
 other side-effects from your medicine, which are
 not mentioned here.

Looking after your tablets

LOOKING after your Tablets
Keep your tablet in a site place where children
cannot see or reach them.
Donot task the tablets after the "use by date
printed on the label carron.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.
This medicinal product does not require any special
storage condition.

PL number 0530/0770

This leaflet was written in March 2006

Tibolone 2.5mg Tablets

WAX

PL 00530/0771

MAX

ibolone 2.5mg Tablets

this leaflet carefully before you start to take your tablets.

It contains important information.

sure about anything, or you want to Know more, ask your holden englacement to group of medicines called homone replacement the more replacement than the more replacement the more replacement than the more doctor or a pharmacist.

Keep this leaflet safe, as you may want to read it again.

About your tablets

Your tablets are called Tibolone 2.5mg Tablets. They are part of a group of drugs called hormone replacement therapy (HRT).

What is in your tablets

- What is in your tablets

 Brokene Zsng (ather lag-dient) and

 Blokene Zsng (ather lag-dient) and

 Lactore Honolydans, Starch Inregulatinized,
 Accordy Palmitate (ESA). Thi sodium Ottate
 Oliphidans, Sodian Lags Salphies
 (offer ingedients).

 Thickness Zsng Tablets are orange white, flat
 bevelled obje tablets, coded "The "on one side and
 bevelled obje tablets, coded "The "on one side and
 Dictore Zsng Tablets are oranged lags and side of 28, 30, 50, 64 and 100 tablets. Not all pack sizes
 are marketed.

If you are not Who makes your tablets

The marketing authorisation holder and manufacturer is N/AX Pharmaceuticals, Albert Basin, Royal Docks, London E16 2QJ.

What your tablets do

Thokne belongs to a group of medicines called hormone replacement therapy of Pin.

Thokne is slightly different to most HET. Instead of the pin.

Thokne is slightly different to most HET. Instead of the pin.

Thokne is slightly different to most HET. Instead of the pin.

Thokne is considered to the pin.

Thokne is made to conventioned estrogen and benefits are similar to conventioned estrogen and benefits are similar to conventioned estrogen. Thokne tablets can relieve symptoms of the mesoquate the charge of this pineth encounting the thought of the bones, if you are at high its of this fractures you have been an analysis of the bones, if you are at high its of their factures are the pineth of the fractures of the pineth of th

Before you take your tablets

Tablets

You should read this section carefully. As well as benefits, 1487 has some risks that you need to consider when you are deciding whether to use it, or whether to across on using it.

I have you using it.

I have you using it.

I have go have had, breast not read to take your tablets 1900 and had not have your tablets 1900 and had not have you start to take your tablets 1900 and had not had not have you tablet a begin of have had not read to have the had not

- earlier visit?

 If you did not then you should do so as soon as possible and before taking these tablets. Your Doctor will then decide whether you should take the tablets or not. He/she may decide to give you different tablets or may wish you to take Tbodone.

What I need to know before taking my medicine

Tibolone will not protect you from pregnancy. You should not take Tibolone until at least 12 months after your last natural menstrual bleed

You should not use recommend the provided by the control and you then harden immentional belief contain lactore. The done should not be taken by children if you have had your womb and corates removed or are being treated with drugs bown as grandomy his releasing lownine (Colomos as grandom) his releasing lownine (Colomos as grandom his releasing lownine types of HET, such as tabeles, poches and gills. Host contain either estrogen or an estrogen and a progestogen with some you have a period, and with some you don't (gento-free HET).

If you are changing over from another type of 16th where you have a prints (2 ant taking Tholma is soon as your proted ends. If you are changing over from a particle five HIT you can also that stagist away if you are being treated for endometricals. You do not not stagist away if you are being treated for endometricals when the contract of the blood of the contract of the contract of the blood dots. It was not also as the contract of Blood dots. It was not also as the Blood dots. It was not also dots Color relatives for blood clots. Close relatives protecting steep grandmother) who has had breast cancer Under disease. Under disease Under disease. Disabetes Californee called systemic lapus erythermatous Epilopy Authman 1 High liked operation Californee C

- Asthma
 Higraine
 Otocolerosis, lehearing disorder)
 If any of the above apply to you:
 Have you told your doctor if not, talk to the doctor as some ayou can before taking. Tholone talkets, the or the may want to do some tosts, or give you more advice about taking. Tholone.

 Safety of HRT

Safety of HRT

As well as benefit, intil some rids which you need to condide when you are deciding whether to meed to condide when you are deciding whether to be ready to the property of the

- If you are worried about any of these things, or if you have had a stroke in the past, talk to your doctor to see if you should take HRT.

If you are worried about any of these things, or if you have had stroke in the part, that by your flyout have had stroke in the part, that by your configured by your had stroke in the part of the pa

- If you're off your feet for a long time because of major surgery, hijaries or liness
 If you have a rare condition called systemic lupus erythematous (SLE)
 If any of these things apply to you, talk to your doctor to see if you should take HRT.

- If any of these timing apply to you, can, w you concern the compare of the compar
- again. Effects on your risk of developing cancer Breast Cancer
- Effects only joint risk of developing cancer. When he had breast cancer in the past, should not take HBT viblorius. It is a state of the had breast cancer in the past, should not take HBT viblorius. The past he had breast cancer in the past, should not take HBT rains past the past of the past
- weetrical for the ordinates in regestion HET 1s.

 General lands of HET, the extra risk of breast cancer feels of HET, the extra risk of breast cancer goes up the longer you take it, but returns to normali within 5 years after scopping HET, your risk of breast cancer is also higher to the second of the second

- cases), If they take estrogen-only HRT for 10 years, the

- figure will be 37 in 100 (i.e. an extra 5 cases). For women who start taking estrogen plus progestogen HRT at age 50 and take it for 5 years, the figure will be 38 in 1000 (i.e. an extra 6 cases).

- 6 casies). "
 If they take estrogen plus progestogen HRT for 10 years, the figure will be 51 in 1000 (i.e. an extra fiyau notice any Anages is year breast, such as dimpting of the sidn changes in the nipple any lumps you can see or feel heldea any applicament to see your doctor as felace and post firms of the sidn of

- a say lumps you can see or feel
 tables an appointment to see your doctor as
 table an appointment to see your doctor as
 tables and the seed of the seed of the seed
 more than the seed of the seed
 more than the seed of the seed
 more than the
 more

- Ovarian cancer
 Ovarian cancer (cancer of the ovaries) is very rare,

but it is serious. It can be difficult to diagnose, because there are often no obvious signs of the disease.

Less have been districted that clining estiogen-only HRT for more than 5 years may increase the sid orward nacrone. It is not yet bronow whether other kinds of HRT increase the risk in the same yet and the side of the si

- Taking other medicines Taking Other interdictions are always and the control to the application of the control to the cont
- infection such as rifampich.

 Medicines used to treat blood clots (thrombosis)
 e.g. warfarin/anticoagulant/blood thinning
 tablets
 Insulin or other drugs used to treat diabetes

How to take your tablet

- I is important to take you tablest only as directed by the doctors or harmacist. It is reportant to take oney day. The economized does in our tablest every day. The economized does in our tablest every day with some water. The search of the control of the doctors with some water. Table your tablest the same time every day. Use in children: Californ should not use Thodonomized the control of th

What to do if you take too

- It is important not to take too many tablets.
 Contact your nearest hospital casualty department or a doctor for advice if you have swallowed too many tablets or if you think a child has swallowed any.

Possible side effects

Please also see the section Safety of HRT in this

- Looking after your tablets Looking after your tablets keep your tablet in a sie place where children cannot see or reach them. On or tase the tables after the 'use by 'date primed on the label corton. This medicinal product does not require any special storage conditions. This medicinal product does not require any special storage conditions. This medicinal product does not require any special storage conditions. This medicinal product does not require any special storage conditions. This medicinal product does not require any special storage conditions. The product does not require any special storage conditions. This medical storage is a special which you no longer need back to your plasmosts. These tablets are only for you. Only a doctor can prescribe them for you stever give them to anyone see even if they have the same symptom as you.

PL number 0530/0771

This leaflet was written in March 2006

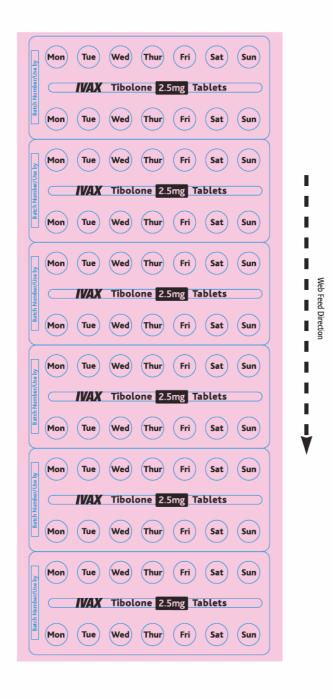
Tibolone 2.5mg Tablets

Labels/Packaging

PL 00530/0708



PL 00530/0708

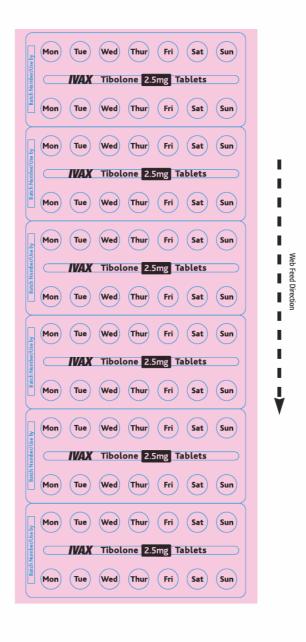


PL 00530/0770



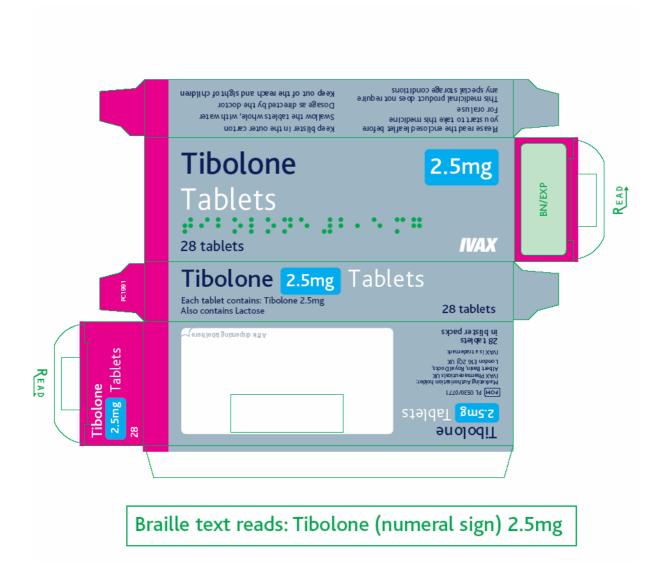
Braille text reads: Tibolone (numeral sign) 2.5mg

PL 00530/0770

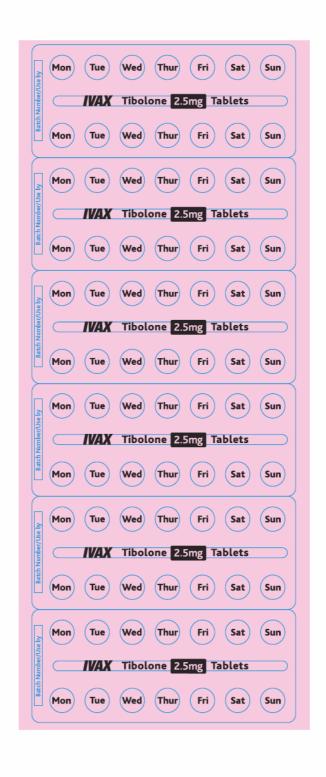


MHRA: PAR - Tibolone 2.5mg Tablets PL 00530/0708, 0770-1

PL 00530/0771



PL 00530/0771



MHRA: PAR – Tibolone 2.5mg Tablets PL 00530/0708, 0770-1

Web Feed Direction