COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Exemestaan Mylan 25 mg, film-coated tablets (exemestane)

# NL/H/4532/001/DC

# Date: 27 February 2023

**This module reflects the scientific discussion for the approval of Exemestaan Mylan 25 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/3911/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.**

Safeguarding public health

MHRA

# Public Assessment Report

# Decentralised Procedure

# Exemestane 25mg Film-coated Tablets
# Xatane 25mg Film-coated Tablets
# Exemin 25mg Film-coated Tablets
# Netamise 25mg Film-coated Tablets

## Exemestane

## UK/H/2363, 3910-1 and 3915/001/DC

## UK licence no: PL 13931/0062, 0064-6

## Chanelle Medical

# LAY SUMMARY

On 24th November 2010, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisations to Chanelle Medical for the medicinal products Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets. The marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 18th February 2011. These medicines are only available on prescription from your doctor.

Exemestane/Xatane/Netamise/Exemin belongs to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women. Reduction in oestrogen levels in the body is way of treating hormone dependent breast cancer.

These products are used to treat hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen. They are also used to treat hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

# TABLE OF CONTENTS

# Module 1

| | |
|---|---|
| **Product Name** | Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | Exemestane |
| **Form** | Film-coated Tablets |
| **Strength** | 25mg |
| **MA Holder** | Chanelle Medical<br>Dublin Road<br>Loughrea<br>County Galway<br>Ireland |
| **RMS** | UK |
| **CMS** | UK/H/236301/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherlands, Poland, Portugal, Romania<br>UK/H/3910/01/DC - Cyprus, Germany, Spain, France, Hungary, Italy, Malta, Poland, Portugal, Romania<br>UK/H/3911/01DC - Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, The Netherland, Norway, Poland, Portugal, Romania, Sweden, Slovak Republic<br>UK/H/3915/01/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherland, Portugal |
| **Procedure Numbers** | UK/H/2363, 3910-1, 3915/01/DC |
| **Timetable** | Day 210 – 24th November 2010 |

# Module 2

## SUMMARY OF PRODUCT CHARACTERISTICS

**1 NAME OF THE MEDICINAL PRODUCT**

Exemestane 25 mg film-coated tablets
Xatane 25 mg film-coated tablets
Exemin 25 mg film-coated tablets
Netamise 25 mg film-coated tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film coated tablet contains 25 mg Exemestane.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated Tablet

White, round biconvex film-coated tablets

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Exemestane is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.

Exemestane is indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy. Efficacy has not been demonstrated in patients with oestrogen receptor negative status.

**4.2 Posology and method of administration**

Oral

Adults and elderly patients

The recommended dose of exemestane is one 25 mg tablet to be taken orally once a day, after a meal. In patients with early breast cancer, treatment with exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by exemestane), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with exemestane should continue until tumour progression is evident.
No dose adjustments are required for patients with hepatic or renal insufficiency (see 5.2).

Children and adolescents

Not recommended for use in children and adolescents.

**4.3 Contraindications**

Exemestane is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients, in pre-menopausal women and in pregnant or breastfeeding women.

**4.4 Special warnings and precautions for use**

Exemestane should not be administered to women with pre-menopausal endocrine status. Therefore, whenever clinically appropriate, the post-menopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

Exemestane should be used with caution in patients with hepatic or renal impairment.

Exemestane is a potent oestrogen lowering agent, and a reduction in bone mineral density and an increased fracture rate has been observed following administration (see section 5.1). During adjuvant treatment with exemestane, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by

exemestane are not available, treatment for osteoporosis should be initiated in at risk patients. Patients treated with exemestane should be carefully monitored.

**4.5 Interaction with other medicinal products and other forms of interaction**

*In vitro* evidence showed that the drug is metabolised through cytochrome P450 (CYP) 3A4 and aldoketoreductases (see 5.2) and does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, the specific inhibition of CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of exemestane.

In an interaction study with rifampicin, a potent CYP450 inducer, at a dose of 600mg daily and a single dose of exemestane 25mg, the AUC of exemestane was reduced by 54% and Cmax by 41%. Since the clinical relevance of this interaction has not been evaluated, the co-administration of drugs, such as rifampicin, anticonvulsants (e.g. phenytoin and carbamazepine) and herbal preparations containing hypericum perforatum (St John's Wort) known to induce CYP3A4 may reduce the efficacy of exemestane.

Exemestane should be used cautiously with drugs that are metabolised via CYP3A4 and have a narrow therapeutic window. There is no clinical experience of the concomitant use of exemestane with other anticancer drugs.

Exemestane should not be coadministered with oestrogen-containing medicines as these would negate its pharmacological action.

**4.6 Pregnancy and lactation**

Pregnancy

No clinical data on exposed pregnancies are available with exemestane. Studies on animals have shown reproductive toxicity (See section 5.3). Exemestane is therefore contraindicated in pregnant women.

Lactation and Breastfeeding

It is not known whether exemestane is excreted into human milk. Exemestane should not be administered to women that are breastfeeding.

Women of perimenopausal status or child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established (see sections 4.3 and 4.4).

**4.7 Effects on ability to drive and use machines**

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of the drug. Patients should be advised that, if these events occur, their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

**4.8 Undesirable effects**

Exemestane was generally well tolerated across all clinical studies conducted with exemestane at a standard dose of 25 mg/day, and undesirable effects were usually mild to moderate.

The withdrawal rate due to adverse events was 7.4% in patients with early breast cancer receiving adjuvant treatment with exemestane following initial adjuvant tamoxifen therapy. The most commonly reported adverse reactions were hot flushes (22%), arthralgia (18%) and fatigue (16%).

The withdrawal rate due to adverse events was 2.8% in the overall patient population with advanced breast cancer. The most commonly reported adverse reactions were hot flushes (14%) and nausea (12%).

Most adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (eg hot flushes).

The reported adverse reactions are listed below by system organ class and by frequency.
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000)

| | |
|---|---|
| ***Metabolism and nutrition disorders:*** | |
| *Common* | Anorexia |
| ***Psychiatric disorders:*** | |
| *Very common* | Insomnia |
| *Common* | Depression |
| ***Nervous system disorders:*** | |
| *Very common* | Headache |
| *Common* | Dizziness, carpal tunnel syndrome |
| *Uncommon* | Somnolence |
| ***Vascular disorders:*** | |
| *Very common* | Hot flushes |
| ***Gastrointestinal disorders:*** | |
| *Very common* | Nausea |
| *Common* | Abdominal pain, vomiting, constipation, dyspepsia, diarrhoea |
| ***Skin and subcutaneous tissue disorders:*** | |
| *Very common* | Increased sweating |
| *Common* | Rash, alopecia |
| ***Musculoskeletal and bone disorders:*** | |
| *Very common* | Joint and musculoskeletal pain (*) |
| *Common* | Osteoporosis, fracture |
| ***General disorders and administration site conditions:*** | |
| *Very common* | Fatigue |
| *Common* | Pain, peripheral oedema |
| *Uncommon* | Asthenia |

(*) Includes: arthralgia, and less frequently pain in limb, osteoarthritis, back pain, arthritis, myalgia and joint stiffness.

***Blood and lymphatic system disorders***
In patients with advanced breast cancer thrombocytopenia and leucopenia have been rarely reported. An occasional decrease in lymphocytes has been observed in approximately 20% of patients receiving exemestane, particularly in patients with pre-existing lymphopenia; however, mean lymphocyte values in these patients did not change significantly over time and no corresponding increase in viral infections was observed. These effects have not been observed in patients treated in early breast cancer studies.
***Hepatobiliary disorders***
Elevation of liver function test parameters including enzymes, bilirubin and alkaline phosphatase have been observed.

The table below presents the frequency of pre-specified adverse events and illnesses in the early breast cancer study (IES), irrespective of causality, reported in patients receiving trial therapy and up to 30 days after cessation of trial therapy.

| Adverse events and illnesses | Exemestane (N = 2249) | Tamoxifen (N = 2279) |
|---|---|---|
| Hot flushes | 491 (21.8%) | 457 (20.1%) |
| Fatigue | 367 (16.3%) | 344 (15.1%) |
| Headache | 305 (13.6%) | 255 (11.2%) |
| Insomnia | 290 (12.9%) | 204 (9.0%) |
| Sweating increased | 270 (12.0%) | 242 (10.6%) |
| Gynaecological | 235 (10.5%) | 340 (14.9%) |
| Dizziness | 224 (10.0%) | 200 (8.8%) |
| Nausea | 200 (8.9%) | 208 (9.1%) |
| Osteoporosis | 116 (5.2%) | 66 (2.9%) |
| Vaginal haemorrhage | 90 (4.0%) | 121 (5.3%) |
| Other primary cancer | 84 (3.6%) | 125 (5.3%) |
| Vomiting | 50 (2.2%) | 54 (2.4%) |
| Visual disturbance | 45 (2.0%) | 53 (2.3%) |
| Thromboembolism | 16 (0.7%) | 42 (1.8%) |
| Osteoporotic fracture | 14 (0.6%) | 12 (0.5%) |
| Myocardial infarction | 13 (0.6%) | 4 (0.2%) |

In the IES study, the frequency of ischemic cardiac events in the exemestane and tamoxifen treatment arms was 4.5% versus 4.2%, respectively. No significant difference was noted for any individual cardiovascular event including hypertension (9.9% versus 8.4%), myocardial infarction (0.6% versus 0.2%) and cardiac failure (1.1% versus 0.7%).

In the IES study, exemestane was associated with a greater incidence of hypercholesterolemia compared with tamoxifen (3.7% vs. 2.1%).

In a separate double blinded, randomized study of postmenopausal women with early breast cancer at low risk treated with exemestane (N=73) or placebo (N=73) for 24 months , exemestane was associated with an average 7-9% mean reduction in plasma HDL-cholesterol, versus a 1% increase on placebo. There was also a 5-6% reduction in apolipoprotein A1 in the exemestane group versus 0-2% for placebo. The effect on the other lipid parameters analysed (total cholesterol, LDL cholesterol, triglycerides, apolipoprotein-B and lipoprotein-a) was very similar in the two treatment groups. The clinical significance of these results is unclear.

In the IES study, gastric ulcer was observed at a higher frequency in the exemestane arm compared to tamoxifen (0.7% versus <0.1%). The majority of patients on exemestane with gastric ulcer received concomitant treatment with non-steroidal anti-inflammatory agents and/or had a prior history.

Adverse reactions from post-marketing experience
Hepatobiliary disorders: Hepatitis, cholestatic hepatitis
Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**4.9 Overdose**

Clinical trials have been conducted with exemestane given up to 800 mg in a single dose to healthy female volunteers and up to 600 mg daily to postmenopausal women with advanced breast cancer; these dosages were well tolerated. The single dose of exemestane that could result in life-threatening symptoms is not known. In rats and dogs, lethality was observed after single oral doses equivalent respectively to 2000 and 4000 times the recommended human dose on a mg/m$^2$ basis. There is no

specific antidote to overdosage and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme inhibitors
ATC: L02BG06
Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, exemestane p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

Exemestane does not possess any progestogenic or oestrogenic activity. A slight androgenic activity, probably due to the 17-hydro derivative, has been observed mainly at high doses. In multiple daily doses trials, exemestane had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other enzymes involved in the steroidogenic pathway.

Glucocorticoid or mineralocorticoid replacements are therefore not needed. A non dose-dependent slight increase in serum LH and FSH levels has been observed even at low doses: this effect is, however, expected for the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in oestrogen levels that stimulate the pituitary secretion of gonadotropins also in postmenopausal women.

Adjuvant Treatment of Early Breast Cancer
In a multicentre, randomised, double-blind study, conducted in 4724 postmenopausal patients with oestrogen-receptor-positive or unknown primary breast cancer, patients who had remained disease-free after receiving adjuvant tamoxifen therapy for 2 to 3 years were randomised to receive 3 to 2 years exemestane (25 mg/day) or tamoxifen (20 or 30 mg/day) to complete a total of 5 years of hormonal therapy.

After a median duration of therapy of about 30 months and a median follow-up of about 52 months, results showed that sequential treatment with exemestane after 2 to 3 years of adjuvant tamoxifen therapy was associated with a clinically and statistically significant improvement in disease-free survival (DFS) compared with continuation of tamoxifen therapy. Analysis showed that in the observed study period exemestane reduced the risk of breast cancer recurrence by 24% compared with tamoxifen (hazard ratio 0.76; p=0.00015). The beneficial effect of exemestane over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Exemestane also significantly reduced the risk of contralateral breast cancer (hazard ratio 0.57, p=0.04158).

In the whole study population, a trend for improved overall survival was observed for exemestane (222 deaths) compared to tamoxifen (262 deaths) with a hazard ratio 0.85 (log-rank test: p = 0.07362), representing a 15% reduction in the risk of death in favor of exemestane. A statistically significant 23% reduction in the risk of dying (hazard ratio for overall survival 0.77; Wald chi square test: p = 0.0069) was observed for exemestane compared to tamoxifen when adjusting for the pre ¯ specified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates). Main efficacy results in all patients (intention to treat population) and oestrogen receptor positive patients are summarised in the table below:

| Endpoint Population | Exemestane Events /N (%) | Tamoxifen Events /N (%) | Hazard Ratio (95% CI) | p-value* |
|---|---|---|---|---|
| **Disease-free survival** [a] | | | | |
| All patients | **354** /2352 (15.1%) | **453** /2372 (19.1%) | 0.76 (0.67-0.88) | 0.00015 |
| ER+ patients | **289** /2023 (14.3%) | **370** /2021 (18.3%) | 0.75 (0.65-0.88) | 0.00030 |
| **Contralateral breast cancer** | | | | |
| All patients | **20** /2352 (0.9%) | **35** /2372 (1.5%) | 0.57 (0.33-0.99) | 0.04158 |
| ER+ patients | **18** /2023 (0.9%) | **33** /2021 (1.6%) | 0.54 (0.30-0.95) | 0.03048 |
| **Breast cancer free survival** [b] | | | | |
| All patients | **289** /2352 (12.3%) | **373** /2372 (15.7%) | 0.76 (0.65-0.89) | 0.00041 |
| ER+ patients | **232** /2023 (11.5%) | **305** /2021 (15.1%) | 0.73 (0.62-0.87) | 0.00038 |
| **Distant recurrence free survival** [c] | | | | |
| All patients | **248** /2352 (10.5%) | **297** /2372 (12.5%) | 0.83 (0.70-0.98) | 0.02621 |
| ER+ patients | **194** /2023 (9.6%) | **242** /2021 (12.0%) | 0.78 (0.65-0.95) | 0.01123 |
| **Overall survival**[d] | | | | |
| All patients | **222** /2352 (9.4%) | **262** /2372 (11.0%) | 0.85 (0.71-1.02) | 0.07362 |
| ER+ patients | **178** /2023 (8.8%) | **211** /2021 (10.4%) | 0.84 (0.68-1.02) | 0.07569 |

* Log-rank test; ER+ patients = oestrogen receptor positive patients;
[a] Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause;
[b] Breast cancer free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or breast cancer death;
[c] Distant recurrence free survival is defined as the first occurrence of distant recurrence or breast cancer death;
[d] Overall survival is defined as occurrence of death from any cause.

In the additional analysis for the subset of patients with oestrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.83 (log-rank test: p = 0.04250), representing a clinically and statistically significant 17% reduction in the risk of dying.

Results from a bone substudy demonstrated that women treated with exemestane following 2 to 3 years of tamoxifen treatment experienced moderate reduction in bone mineral density. In the overall study, the treatment emergent fracture incidence evaluated during the 30 months treatment period was higher in patients treated with exemestane compared with tamoxifen (4.5% and 3.3% correspondingly, p=0.038).

Results from an endometrial substudy indicate that after 2 years of treatment there was a median 33% reduction of endometrial thickness in the exemestane -treated patients compared with no notable variation in the tamoxifen-treated patients. Endometrial thickening, reported at the start of study treatment, was reversed to normal (< 5 mm) for 54% of patients treated with exemestane.

Treatment of Advanced Breast Cancer

In a randomised peer reviewed controlled clinical trial, exemestane at the daily dose of 25 mg has demonstrated statistically significant prolongation of survival, Time to Progression (TTP), Time to Treatment Failure (TTF) as compared to a standard hormonal treatment with megestrol acetate in postmenopausal patients with advanced breast cancer that had progressed following, or during, treatment with tamoxifen either as adjuvant therapy or as first-line treatment for advanced disease.

## 5.2 Pharmacokinetic properties

**Absorption**:
After oral administration exemestane is absorbed rapidly. The fraction of the dose absorbed from the gastrointestinal tract is high. The absolute bioavailability in humans is unknown, although it is anticipated to be limited by an extensive first pass effect. A similar effect resulted in an absolute bioavailability in rats and dogs of 5%. After a single dose of 25 mg, maximum plasma levels of 18 ng/ml are reached after 2 hours. Concomitant intake with food increases the bioavailability by 40%.

**Distribution**:
The volume of distribution of exemestane, not corrected for the oral bioavailability, is ca 20000 L. The kinetics is linear and the terminal elimination half-life is 24 h. Binding to plasma proteins is 90% and is concentration independent. Exemestane and its metabolites do not bind to red blood cells.
Exemestane does not accumulate in an unexpected way after repeated dosing.

**Metabolism and excretion**:
Exemestane is metabolised by oxidation of the methylene moiety on the 6 position by CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane is ca 500 l/h, not corrected for the oral bioavailability.
The metabolites are inactive or the inhibition of aromatase is less than the parent compound.
The amount excreted unchanged in urine is 1% of the dose. In urine and faeces equal amounts (40%) of $^{14}C$-labeled exemestane were eliminated within a week.

**Special populations**

**Age:** No significant correlation between the systemic exposure of exemestane and the age of subjects has been observed.

**Renal insufficiency:**
In patients with severe renal impairment ($CL_{cr} \leq 30$ ml/min) the systemic exposure to exemestane was 2 times higher compared with healthy volunteers.
Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

**Hepatic insufficiency:**
In patients with moderate or severe hepatic impairment the exposure of exemestane is 2-3 fold higher compared with healthy volunteers. Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

## 5.3 Preclinical safety data

**Toxicological studies:** Findings in the repeat dose toxicology studies in rat and dog were generally attributable to the pharmacological activity of exemestane, such as effects on reproductive and accessory organs. Other toxicological effects (on liver, kidney or central nervous system) were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

**Mutagenicity:** Exemestane was not genotoxic in bacteria (Ames test), in V79 Chinese hamster cells, in rat hepatocytes or in the mouse micronucleus assay. Although exemestane was clastogenic in lymphocytes *in vitro*, it was not clastogenic in two *in vivo* studies.

**Reproductive toxicology***:* Exemestane was embryotoxic in rats and rabbits at systemic exposure levels similar to those obtained in humans at 25 mg/day. There was no evidence of teratogenicity.

**Carcinogenicity:** In a two-year carcinogenicity study in female rats, no treatment-related tumors were observed. In male rats the study was terminated on week 92, because of early death by chronic nephropathy. In a two-year carcinogenicity study in mice, an increase in the incidence of hepatic neoplasms in both genders was observed at the intermediate and high doses (150 and 450 mg/kg/day). This finding is considered to be related to the induction of hepatic microsomal enzymes, an effect observed in mice but not in clinical studies. An increase in the incidence of renal tubular adenomas was also noted in male mice at the high dose (450 mg/kg/day). This change is considered to be species- and gender-specific and occurred at a dose which represents 63-fold greater exposure than occurs at the human therapeutic dose. None of these observed effects is considered to be clinically relevant to the treatment of patients with exemestane.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet Core:
Silica, colloidal anhydrous,
Crospovidone,
Hypromellose 5cP,
Magnesium Stearate,
Mannitol,
Microcrystalline Cellulose,
Polysorbate 80,
Sodium Starch Glycolate (Type A).

Film-coating:
Hypromellose 5cP,
Macrogol,
Talc,
Titanium Dioxide (E171).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 Years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Blister Packs of white PVC/PVDC – aluminium blisters. Pack sizes 14, 15, 20, 30, 60, 90, 100 and 120.

Not all pack sizes will be marketed.

### 6.6 Special precautions for disposal

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

## 7 MARKETING AUTHORISATION HOLDER

Chanelle Medical, Loughrea, Co. Galway, Ireland.

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 13931/0062
PL 13931/0064
PL 13931/0065
PL 13931/0066

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/02/2011

## 10 DATE OF REVISION OF THE TEXT

18/02/2011

# Module 3

## PACKAGE LEAFLET: INFORMATION FOR THE USER

## Exemestane 25 mg Film-coated Tablets (Exemestane)

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

**In this leaflet:**


### 1. What Exemestane is and what it is used for

Your medicine is called Exemestane. Exemestane belongs to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women. Reduction in oestrogen levels in the body is a way of treating hormone dependent breast cancer.

Exemestane is used to treat hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen.

Exemestane is also used to treat hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

### 2. Before you take Exemestane

**Do not take Exemestane**
- if you are or have previously been allergic (hypersensitive) to exemestane (the active ingredient in Exemestane) or any of the other ingredients of Exemestane. See section 6 ("What Exemestane contains") for full list of other ingredients.
- if you have **not** already been through 'the menopause', i.e. you are still having your monthly period.
- if you are pregnant, likely to be pregnant or breastfeeding.

**Take special care with Exemestane**
- Before treatment with Exemestane, your doctor may want to take blood samples to make sure you have reached the menopause.
- Before taking Exemestane, tell your doctor if you have problems with your liver or kidneys.
- Tell your doctor if you have a history or are suffering from any condition which affects the strength of your bones. Your doctor may want to measure your bone density before and during the treatment of Exemestane. This is because drugs of this class lower the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength.

**Taking other medicines**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Exemestane should not be given at the same time as hormone replacement therapy (HRT).
The following medicines should be used cautiously when taking Exemestane. Let your doctor know if you are taking medicines such as:
- rifampicin (an antibiotic),
- carbamazepine or phenytoin (anticonvulsants used to treat epilepsy),
- herbal remedy St Johns Wort (Hypericum perforatum), or preparations containing it.

**Pregnancy and breast-feeding**
Do not take Exemestane if you are pregnant or breastfeeding.
If you are pregnant or think you might be, tell your doctor.
Discuss contraception with your doctor if there is any possibility that you may become pregnant.

**Driving and using machines**
If you feel drowsy, dizzy or weak whilst taking Exemestane, you should not attempt to drive or operate machinery.

### 3. How to take Exemestane

**Adults and the elderly**
Exemestane tablets should be taken by mouth after a meal at approximately the same time each day. Your doctor will tell you how to take Exemestane and for how long. The recommended dose is one 25 mg tablet daily.
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you need to go to the hospital whilst taking Exemestane, let the medical staff know what medication you are taking.

**Children and adolescents below 18 years**
Exemestane is not suitable for use in children and adolescents below 18 years.

**If you take more Exemestane than you should**
If too many tablets are taken by accident, contact your doctor at once or go straight to the nearest hospital casualty department. Show them the pack of exemestane tablets.

**If you forget to take Exemestane**
Do not take a double dose to make up for a forgotten tablet. If you forget to take your tablet, take it as soon as you remember. If it is nearly time for the next dose, take it at the usual time.

**If you stop taking Exemestane**
Do not stop treatment without consulting your doctor. If you stop the treatment your symptoms might reappear.

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

## 4. Possible side effects

Like all medicines, Exemestane can cause side effects, although not everybody gets them. In general, Exemestane is well tolerated and the following side effects observed in patients treated with Exemestane are mainly mild or moderate in nature. Most of the side effects are associated with a shortage of oestrogen (e.g. hot flushes).

**Very common side effects, (affecting more than 1 person in 10):**
- Difficulty sleeping
- Headache
- Hot flushes
- Feeling sick
- Increased sweating
- Muscle and joint pain (including osteoarthritis, back pain, arthritis and joint stiffness)
- Tiredness

**Common side effects, (affecting between 1 to 10 people in 100):**
- Loss of appetite
- Depression
- Dizziness, carpal tunnel syndrome (a combination of pins and needles, numbness and pain affecting all of the hand except the little finger)
- Stomach ache, vomiting (being sick), constipation, indigestion, diarrhoea
- Skin rash, hair loss
- Thinning of bones which might decrease their strength (osteoporosis), leading to bone fractures (breaks or cracks) in some cases
- Pain, swollen hands and feet

**Uncommon side effects, (affecting between 1 to 10 people in 1000):**
- Drowsiness
- Muscle weakness

Inflammation of the liver (hepatitis) may occur. Symptoms include feeling generally unwell, nausea, jaundice, (yellowing of the skin and eyes), itching, right sided abdominal pain and loss of appetite. Contact your doctor promptly if you think you have any of these symptoms.

If you have any blood tests done, it may be noticed that there are changes in your liver function. Changes in the amount of certain blood cells (lymphocytes) and platelets circulating in your blood may occur, especially in patients with a pre-existing lymphopenia (reduced lymphocytes in the blood).
If any side effects get serious or if you notice any side effect not listed on this leaflet, please tell your doctor or your pharmacist as soon as possible.

## 5. How to store Exemestane

**Keep out of the reach and sight of children.**

- This medicinal product does not require any special storage conditions.
- Do not use Exemestane after expiry date which is stated on the outer carton and the blister after EXP. The expiry date refers to the last day of the month.
- Exemestane should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

**What Exemestane contains:**
The active ingredient is Exemestane. Each film-coated tablet contains 25 mg of Exemestane.

The other ingredients are:
Tablet Core: Silica, colloidal anhydrous, Crospovidone, Hypromellose 5cP, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polysorbate 80 and Sodium Starch Glycolate (Type A).
Film-coating: Hypromellose 5cP, Macrogol, Talc and Titanium Dioxide (E171).

**What Exemestane looks like and contents of the pack**
Exemestane 25 mg Film-coated Tablets are white, round biconvex film-coated tablets
Exemestane 25 mg Film-coated Tablets are available in blister packs of 14, 15, 20, 30, 60, 90, 100 and 120.
Not all pack sizes will be marketed.

**Marketing Authorisation Holder and Manufacturer**
The marketing authorisation holder is Chanelle Medical, Loughrea, Co Galway, Ireland.
The manufacturer is Remedica Ltd, Limassol Industrial Estate, Limassol Cyprus, EU.

**This leaflet was prepared in:** January 2011

P-18/0690/01-d

# PACKAGE LEAFLET: INFORMATION FOR THE USER
# Xatane 25 mg Film-coated Tablets (Exemestane)

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

**In this leaflet:**


## 1. What Xatane is and what it is used for
Your medicine is called Xatane. Xatane belongs to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women. Reduction in oestrogen levels in the body is a way of treating hormone dependent breast cancer.

Xatane is used to treat hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen.

Xatane is also used to treat hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

## 2. Before you take Xatane

**Do not take Xatane**
- if you are or have previously been allergic (hypersensitive) to exemestane (the active ingredient in Xatane) or any of the other ingredients of Xatane. See section 6 ("What Xatane contains") for full list of other ingredients.
- if you have **not** already been through 'the menopause', i.e. you are still having your monthly period.
- if you are pregnant, likely to be pregnant or breastfeeding.

**Take special care with Xatane**
- Before treatment with Xatane, your doctor may want to take blood samples to make sure you have reached the menopause.
- Before taking Xatane, tell your doctor if you have problems with your liver or kidneys.
- Tell your doctor if you have a history or are suffering from any condition which affects the strength of your bones. Your doctor may want to measure your bone density before and during the treatment of Xatane. This is because drugs of this class lower the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength.

**Taking other medicines**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Xatane should not be given at the same time as hormone replacement therapy (HRT).
The following medicines should be used cautiously when taking Xatane. Let your doctor know if you are taking medicines such as:
- rifampicin (an antibiotic),
- carbamazepine or phenytoin (anticonvulsants used to treat epilepsy),
- herbal remedy St Johns Wort (Hypericum perforatum), or preparations containing it.

**Pregnancy and breast-feeding**
Do not take Xatane if you are pregnant or breastfeeding.
If you are pregnant or think you might be, tell your doctor.
Discuss contraception with your doctor if there is any possibility that you may become pregnant.

**Driving and using machines**
If you feel drowsy, dizzy or weak whilst taking Xatane, you should not attempt to drive or operate machinery.

## 3. How to take Xatane

**Adults and the elderly**
Xatane tablets should be taken by mouth after a meal at approximately the same time each day. Your doctor will tell you how to take Xatane and for how long. The recommended dose is one 25 mg tablet daily.
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you need to go to the hospital whilst taking Xatane, let the medical staff know what medication you are taking.

**Children and adolescents below 18 years**
Xatane is not suitable for use in children and adolescents below 18 years.

**If you take more Xatane than you should**
If too many tablets are taken by accident, contact your doctor at once or go straight to the nearest hospital casualty department. Show them the pack of Xatane tablets.

**If you forget to take Xatane**
Do not take a double dose to make up for a forgotten tablet. If you forget to take your tablet, take it as soon as you remember. If it is nearly time for the next dose, take it at the usual time.

**If you stop taking Xatane**
Do not stop treatment without consulting your doctor. If you stop the treatment your symptoms might reappear.

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

## 4. Possible side effects

Like all medicines, Xatane can cause side effects, although not everybody gets them. In general, Xatane is well tolerated and the following side effects observed in patients treated with Xatane are mainly mild or moderate in nature. Most of the side effects are associated with a shortage of oestrogen (e.g. hot flushes).

**Very common side effects, (affecting more than 1 person in 10):**
- Difficulty sleeping
- Headache
- Hot flushes
- Feeling sick
- Increased sweating
- Muscle and joint pain (including osteoarthritis, back pain, arthritis and joint stiffness)
- Tiredness

**Common side effects, (affecting between 1 to 10 people in 100):**
- Loss of appetite
- Depression
- Dizziness, carpal tunnel syndrome (a combination of pins and needles, numbness and pain affecting all of the hand except the little finger)
- Stomach ache, vomiting (being sick), constipation, indigestion, diarrhoea
- Skin rash, hair loss
- Thinning of bones which might decrease their strength (osteoporosis), leading to bone fractures (breaks or cracks) in some cases
- Pain, swollen hands and feet

**Uncommon side effects, (affecting between 1 to 10 people in 1000):**
- Drowsiness
- Muscle weakness

Inflammation of the liver (hepatitis) may occur. Symptoms include feeling generally unwell, nausea, jaundice (yellowing of the skin and eyes), itching, right sided abdominal pain and loss of appetite. Contact your doctor promptly if you think you have any of these symptoms.

If you have any blood tests done, it may be noticed that there are changes in your liver function. Changes in the amount of certain blood cells (lymphocytes) and platelets circulating in your blood may occur, especially in patients with a pre-existing lymphopenia (reduced lymphocytes in the blood).
If any side effects get serious or if you notice any side effect not listed on this leaflet, please tell your doctor or your pharmacist as soon as possible.

## 5. How to store Xatane

**Keep out of the reach and sight of children.**

- This medicinal product does not require any special storage conditions.
- Do not use Xatane after expiry date which is stated on the outer carton and the blister after EXP. The expiry date refers to the last day of the month.
- Xatane should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

**What Xatane contains:**
The active ingredient is Exemestane. Each film-coated tablet contains 25 mg of Exemestane.

The other ingredients are:
Tablet Core: Silica, colloidal anhydrous, Crospovidone, Hypromellose 5cP, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polysorbate 80 and Sodium Starch Glycolate (Type A).
Film-coating: Hypromellose 5cP, Macrogol, Talc and Titanium Dioxide (E171).

**What Xatane looks like and contents of the pack**
Xatane 25 mg Film-coated Tablets are white, round biconvex film-coated tablets
Xatane 25 mg Film-coated Tablets are available in blister packs of 14, 15, 20, 30, 60, 90, 100 and 120.
Not all pack sizes will be marketed.

**Marketing Authorisation Holder and Manufacturer**
The marketing authorisation holder is Chanelle Medical, Loughrea, Co Galway, Ireland.
The manufacturer is Remedica Ltd, Limassol Industrial Estate, Limassol Cyprus, EU.
**The distributor is Chanelle Medical, U.K. Ltd.**

**This leaflet was prepared in:** January 2011 IO/9690/01-d

## PACKAGE LEAFLET: INFORMATION FOR THE USER

Exemin 25 mg Film-coated Tablets
**(Exemestane)**

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

**In this leaflet:**


### 1. What *Exemin 25 mg film-coated tablets* is and what it is used for

Your medicine is called *Exemin 25 mg film-coated tablets*. *Exemin 25 mg film-coated tablets* belong to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women. Reduction in oestrogen levels in the body is a way of treating hormone dependent breast cancer.

*Exemin 25 mg film-coated tablets* are used to treat hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen.

*Exemin 25 mg film-coated tablets* are also used to treat hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

### 2. Before you take *Exemin 25 mg film-coated tablets*

**Do not take *Exemin 25 mg film-coated tablets***

if you are or have previously been allergic (hypersensitive) to exemestane (the active ingredient in *Exemin 25 mg film-coated tablets*) or any of the other ingredients of Exemin 25 mg film-coated tablets. See section 6 ("What *Exemin 25 mg film-coated tablets* contains") for full list of other ingredients.

- if you have **not** already been through 'the menopause', i.e. you are still having your monthly period.
- if you are pregnant, likely to be pregnant or breastfeeding.

**Take special care with**
- Before treatment with *Exemin 25 mg film-coated tablets*, your doctor may want to take blood samples to make sure you have reached the menopause.

- Before taking *Exemin 25 mg film-coated tablets*, tell your doctor if you have problems with your liver or kidneys.
- Tell your doctor if you have a history or are suffering from any condition which affects the strength of your bones. Your doctor may want to measure your bone density before and during the treatment of *Exemin 25 mg film-coated tablets*. This is because drugs of this class lower the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength.

**Taking other medicines**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
*Exemin 25 mg film-coated tablets* should not be given at the same time as hormone replacement therapy (HRT).
The following medicines should be used cautiously when taking *Exemin 25 mg film-coated tablets*.
Let your doctor know if you are taking medicines such as:
- rifampicin (an antibiotic),
- carbamazepine or phenytoin (anticonvulsants used to treat epilepsy),
- herbal remedy St Johns Wort (Hypericum perforatum), or preparations containing it.

**Pregnancy and breast-feeding**
Do not take *Exemin 25 mg film-coated tablets* if you are pregnant or breastfeeding.
If you are pregnant or think you might be, tell your doctor.
Discuss contraception with your doctor if there is any possibility that you may become pregnant.

**Driving and using machines**
If you feel drowsy, dizzy or weak whilst taking *Exemin 25 mg film-coated tablets*, you should not attempt to drive or operate machinery.

## 3. How to take *Exemin 25 mg film-coated tablets*

**Adults and the elderly**
*Exemin* tablets should be taken by mouth after a meal at approximately the same time each day. Your doctor will tell you how to take Exemin and for how long. The recommended dose is one 25 mg tablet daily.
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you need to go to the hospital whilst taking *Exemin*, let the medical staff know what medication you are taking.

**Children and adolescents below 18 years**
*Exemin* is not suitable for use in children and adolescents below 18 years.

**If you take more *Exemin 25 mg film-coated tablets* than you should**
If too many tablets are taken by accident, contact your doctor at once or go straight to the nearest hospital casualty department. Show them the pack of *Exemin* tablets.

**If you forget to take *Exemin 25 mg film-coated tablets***
Do not take a double dose to make up for a forgotten tablet.
If you forget to take your tablet, take it as soon as you remember. If it is nearly time for the next dose, take it at the usual time.

**If you stop taking *Exemin 25 mg film-coated tablets***
Do not stop treatment without consulting your doctor. If you stop the treatment your symptoms might reappear.

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

## 4. Possible side effects

Like all medicines, *Exemin 25 mg film-coated tablets* can cause side effects, although not everybody gets them. In general, *Exemin* is well tolerated and the following side effects observed in patients treated with *Exemin* are mainly mild or moderate in nature. Most of the side effects are associated with a shortage of oestrogen (e.g. hot flushes).

**Very common side effects, (affecting more than 1 person in 10):**
- Difficulty sleeping
- Headache
- Hot flushes
- Feeling sick
- Increased sweating
- Muscle and joint pain (including osteoarthritis, back pain, arthritis and joint stiffness)
- Tiredness

**Common side effects, (affecting between 1 to 10 people in 100):**
- Loss of appetite
- Depression
- Dizziness, carpal tunnel syndrome (a combination of pins and needles, numbness and pain affecting all of the hand except the little finger)
- Stomach ache, vomiting (being sick), constipation, indigestion, diarrhoea
- Skin rash, hair loss
- Thinning of bones which might decrease their strength (osteoporosis), leading to bone fractures (breaks or cracks) in some cases
- Pain, swollen hands and feet

**Uncommon side effects, (affecting between 1 to 10 people in 1000):**
- Drowsiness
- Muscle weakness

Inflammation of the liver (hepatitis) may occur. Symptoms include feeling generally unwell, nausea, jaundice (yellowing of the skin and eyes), itching, right sided abdominal pain and loss of appetite. Contact your doctor promptly if you think you have any of these symptoms.

If you have any blood tests done, it may be noticed that there are changes in your liver function. Changes in the amount of certain blood cells (lymphocytes) and platelets circulating in your blood may occur, especially in patients with a pre-existing lymphopenia (reduced lymphocytes in the blood).
If any side effects get serious or if you notice any side effect not listed on this leaflet, please tell your doctor or your pharmacist as soon as possible.

## 5. How to store *Exemin 25 mg film-coated tablets*

**Keep out of the reach and sight of children.**

- This medicinal product does not require any special storage conditions.
- Do not use *Exemin 25 mg film-coated tablets* after expiry date which is stated on the outer carton and the blister after EXP. The expiry date refers to the last day of the month.
- *Exemin 25 mg film-coated tablets* should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

**What *Exemin 25 mg film-coated tablets* contains:**
The active ingredient is Exemestane.
Each film-coated tablet contains 25 mg of Exemestane.

The other ingredients are:
Tablet Core: Silica, colloidal anhydrous, Crospovidone, Hypromellose 5cP, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polysorbate 80 and Sodium Starch Glycolate (Type A).
Film-coating: Hypromellose 5cP, Macrogol, Talc and Titanium Dioxide (E171).

**What *Exemin 25 mg film-coated tablets* looks like and contents of the pack**
*Exemin 25 mg film-coated tablets* are white, round biconvex film-coated tablets
*Exemin 25 mg film-coated tablets* are available in blister packs of 14, 15, 20, 30, 60, 90, 100 and 120 tablets.

Not all pack sizes will be marketed.

**Marketing Authorisation Holder and Manufacturer**
The marketing authorisation holder is Chanelle Medical, Loughrea, Co. Galway, Ireland.
The manufacturer is Remedica Limited, Limassol Industrial Estate, P.O. Box 51706, CY-3508 Limassol, Cyprus.

**This medicinal product is authorised in the Member States of the EEA under the following names:**

| | |
|---|---|
| | |

**This leaflet was prepared in:** MM/YYYY

# PACKAGE LEAFLET: INFORMATION FOR THE USER
# Netamise 25 mg Film-coated Tablets (Exemestane)

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

**In this leaflet:**


## 1. What Netamise is and what it is used for
Your medicine is called Netamise. Netamise belongs to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women. Reduction in oestrogen levels in the body is a way of treating hormone dependent breast cancer.

Netamise is used to treat hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen.

Netamise is also used to treat hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

## 2. Before you take Netamise

**Do not take Netamise**
- if you are or have previously been allergic (hypersensitive) to exemestane (the active ingredient in Netamise) or any of the other ingredients of Netamise. See section 6 ("What Netamise contains") for full list of other ingredients.
- if you have **not** already been through 'the menopause', i.e. you are still having your monthly period.
- if you are pregnant, likely to be pregnant or breastfeeding.

**Take special care with Netamise**
- Before treatment with Netamise, your doctor may want to take blood samples to make sure you have reached the menopause.
- Before taking Netamise, tell your doctor if you have problems with your liver or kidneys.
- Tell your doctor if you have a history or are suffering from any condition which affects the strength of your bones. Your doctor may want to measure your bone density before and during the treatment of Netamise. This is because drugs of this class lower the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength.

**Taking other medicines**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Netamise should not be given at the same time as hormone replacement therapy (HRT).
The following medicines should be used cautiously when taking Netamise. Let your doctor know if you are taking medicines such as:
- rifampicin (an antibiotic),
- carbamazepine or phenytoin (anticonvulsants used to treat epilepsy),
- herbal remedy St Johns Wort (Hypericum perforatum), or preparations containing it.

**Pregnancy and breast-feeding**
Do not take Netamise if you are pregnant or breastfeeding.
If you are pregnant or think you might be, tell your doctor.
Discuss contraception with your doctor if there is any possibility that you may become pregnant.

**Driving and using machines**
If you feel drowsy, dizzy or weak whilst taking Netamise, you should not attempt to drive or operate machinery.

## 3. How to take Netamise

**Adults and the elderly**
Netamise tablets should be taken by mouth after a meal at approximately the same time each day. Your doctor will tell you how to take Netamise and for how long. The recommended dose is one 25 mg tablet daily.
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you need to go to the hospital whilst taking Netamise, let the medical staff know what medication you are taking.

**Children and adolescents below 18 years**
Netamise is not suitable for use in children and adolescents below 18 years.

**If you take more Netamise than you should**
If too many tablets are taken by accident, contact your doctor at once or go straight to the nearest hospital casualty department. Show them the pack of Netamise tablets.

**If you forget to take Netamise**
Do not take a double dose to make up for a forgotten tablet. If you forget to take your tablet, take it as soon as you remember. If it is nearly time for the next dose, take it at the usual time.

**If you stop taking Netamise**
Do not stop treatment without consulting your doctor. If you stop the treatment your symptoms might reappear.

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

## 4. Possible side effects

Like all medicines, Netamise can cause side effects, although not everybody gets them. In general, Netamise is well tolerated and the following side effects observed in patients treated with Netamise are mainly mild or moderate in nature. Most of the side effects are associated with a shortage of oestrogen (e.g. hot flushes).

**Very common side effects, (affecting more than 1 person in 10):**
- Difficulty sleeping
- Headache
- Hot flushes
- Feeling sick
- Increased sweating
- Muscle and joint pain (including osteoarthritis, back pain, arthritis and joint stiffness)
- Tiredness

**Common side effects, (affecting between 1 to 10 people in 100):**
- Loss of appetite
- Depression
- Dizziness, carpal tunnel syndrome (a combination of pins and needles, numbness and pain affecting all of the hand except the little finger)
- Stomach ache, vomiting (being sick), constipation, indigestion, diarrhoea
- Skin rash, hair loss
- Thinning of bones which might decrease their strength (osteoporosis), leading to bone fractures (breaks or cracks) in some cases
- Pain, swollen hands and feet

**Uncommon side effects, (affecting between 1 to 10 people in 1000):**
- Drowsiness
- Muscle weakness

Inflammation of the liver (hepatitis) may occur. Symptoms include feeling generally unwell, nausea, jaundice (yellowing of the skin and eyes), itching, right sided abdominal pain and loss of appetite. Contact your doctor promptly if you think you have any of these symptoms.

If you have any blood tests done, it may be noticed that there are changes in your liver function. Changes in the amount of certain blood cells (lymphocytes) and platelets circulating in your blood may occur, especially in patients with a pre-existing lymphopenia (reduced lymphocytes in the blood).
If any side effects get serious or if you notice any side effect not listed on this leaflet, please tell your doctor or your pharmacist as soon as possible.

## 5. How to store Netamise

**Keep out of the reach and sight of children.**

- This medicinal product does not require any special storage conditions.
- Do not use Netamise after expiry date which is stated on the outer carton and the blister after EXP. The expiry date refers to the last day of the month.
- Netamise should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

**What Netamise contains:**
The active ingredient is Exemestane. Each film-coated tablet contains 25 mg of Exemestane.

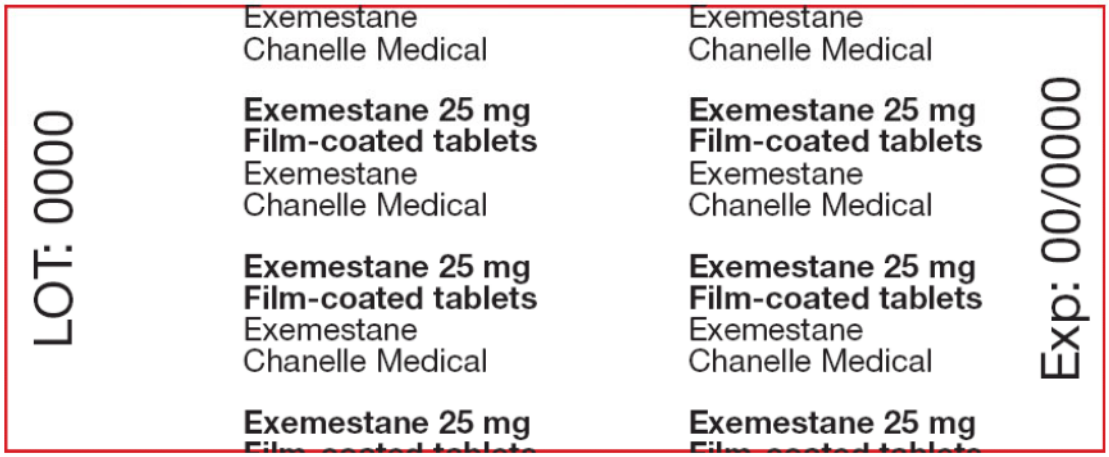
The other ingredients are:
Tablet Core: Silica, colloidal anhydrous, Crospovidone, Hypromellose 5cP, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polysorbate 80 and Sodium Starch Glycolate (Type A).
Film-coating: Hypromellose 5cP, Macrogol, Talc and Titanium Dioxide (E171).

**What Netamise looks like and contents of the pack**
Netamise 25 mg Film-coated Tablets are white, round biconvex film-coated tablets
Netamise 25 mg Film-coated Tablets are available in blister packs of 14, 15, 20, 30, 60, 90, 100 and 120.
Not all pack sizes will be marketed.

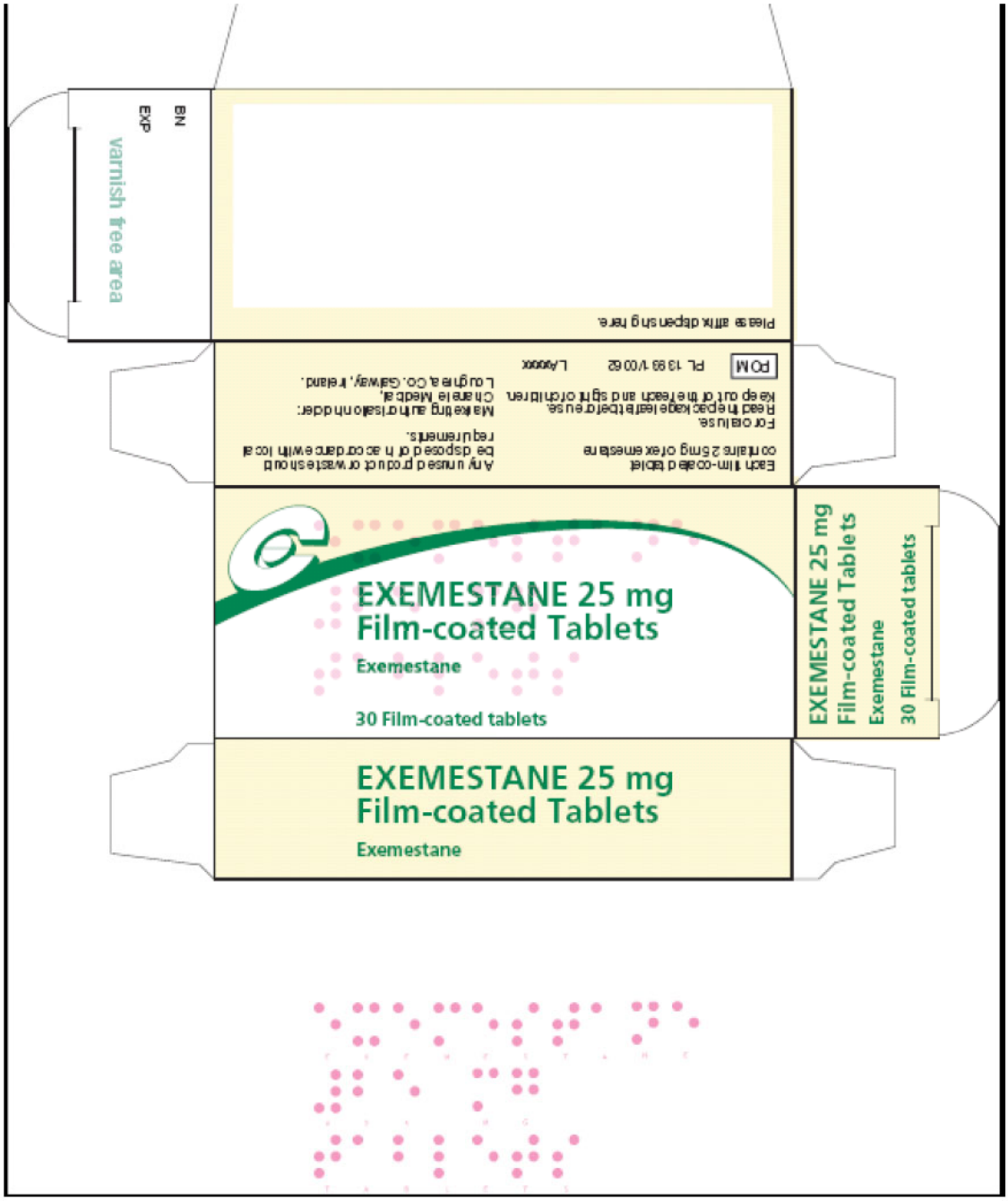
**Marketing Authorisation Holder and Manufacturer**
The marketing authorisation holder is Chanelle Medical, Loughrea, Co Galway, Ireland.
The manufacturer is Remedica Ltd, Limassol Industrial Estate, Limassol Cyprus, EU.

**This leaflet was prepared in:** January 2011 10/9690/81d

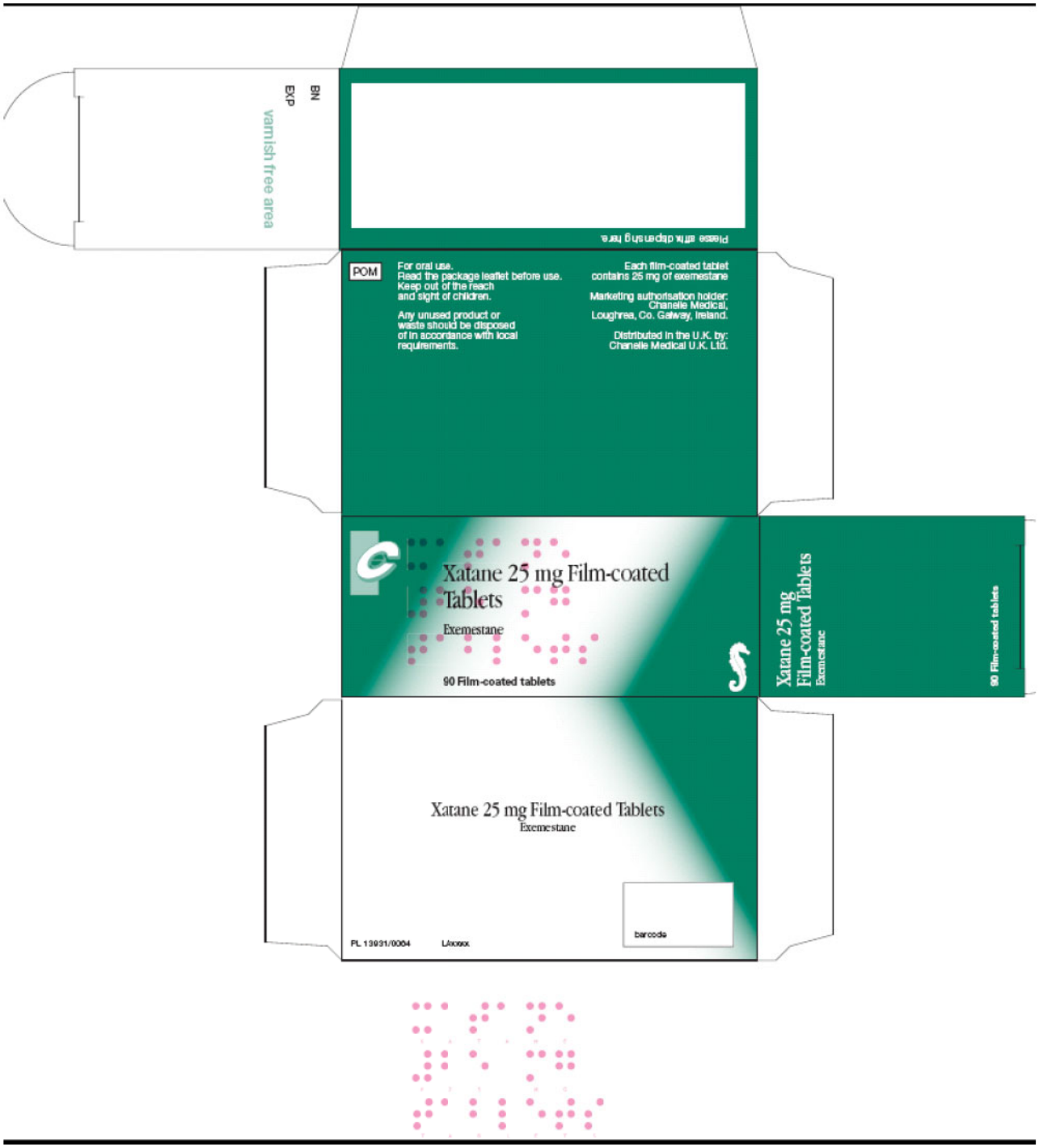
# Module 4
# Labelling

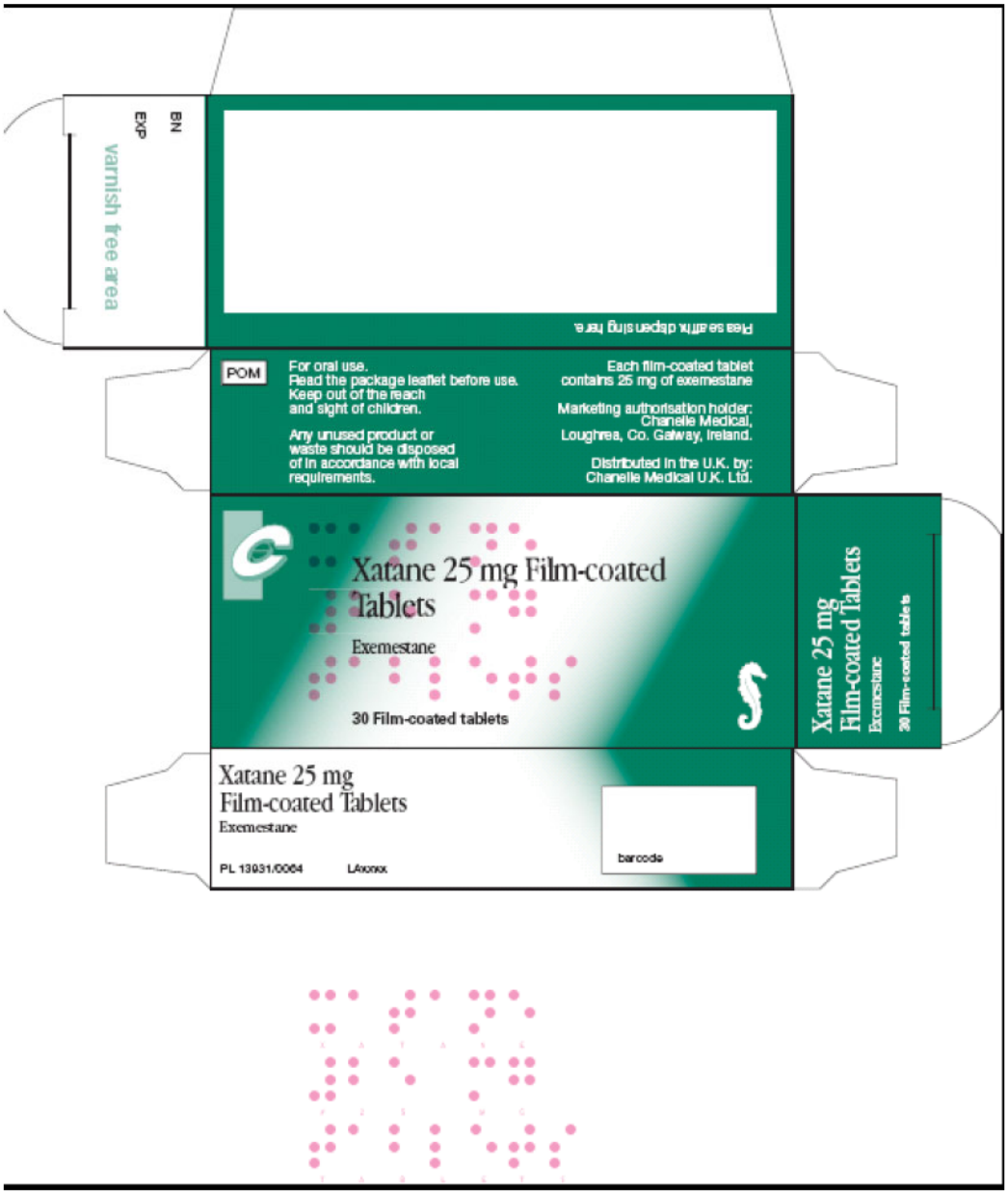



varnish free area
Exp
BN
Please affix dispensing here.
PL 13931/0052
LXXXXX
Exemestane
Each film-coated tablet
contains 25 mg of exemestane
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Any unused product or waste should
be disposed of in accordance with local
requirements.
Marketing authorisation holder:
Crinetics Medical,
Loughrea, Co. Galway Ireland
EXEMESTANE 25 mg
Film-coated Tablets
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane
100 Film-coated tablets
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane
100 Film-coated tablets
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane


varnish free area
BN
EXP
Please affix dispensing here.
PL 13393/0062
PO M
L/xxxxx
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Each film-coated tablet
contains 25mg of exemestane
Any unused product or waste should
be disposed of in accordance with local
requirements.
Marketing authorisation holder:
Chanelle Medical,
Loughrea Co. Galway, Ireland.
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane
30 Film-coated tablets
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane
30 Film-coated tablets
EXEMESTANE 25 mg
Film-coated Tablets
Exemestane


LOT: 0000
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Xatane 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Exp: 00/00


BN
EXP
varnish free area
Please affix dispensing here
POM
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Any unused product or waste should be disposed of in accordance with local requirements.
Each film-coated tablet contains 25 mg of exemestane
Marketing authorisation holder:
Chanelle Medical,
Loughrea, Co. Galway, Ireland.
Distributed in the U.K. by:
Chanelle Medical U.K. Ltd.
Xatane 25 mg Film-coated Tablets
Exemestane
90 Film-coated tablets
Xatane 25 mg Film-coated Tablets
Exemestane
Xatane 25 mg Film-coated Tablets
Exemestane
90 Film-coated tablets
PL 13931/0004
Lxxxxx
barcode


BN
EXP
varnish free area
Tear earth opening here.
POM
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Any unused product or waste should be disposed of in accordance with local requirements.
Each film-coated tablet contains 25 mg of exemestane
Marketing authorisation holder:
Chanelle Medical,
Loughrea, Co. Galway, Ireland.
Distributed in the U.K. by:
Chanelle Medical U.K. Ltd.
Xatane 25 mg Film-coated Tablets
Exemestane
30 Film-coated tablets
Xatane 25 mg Film-coated Tablets
Exemestane
30 Film-coated tablets
Xatane 25 mg
Film-coated Tablets
Exemestane
PL 13931/0064
LAxxxx
barcode

## PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING {CARTON}

### 1. Name of the medicinal product

Exemin 25 mg film-coated tablets
Exemestane

### 2. Statement of active substance(s)

Each film-coated tablet contains 25 mg of exemestane

### 3. List of excipients

### 4. Pharmaceutical form and contents

Film-coated tablets

14 tablets
15 tablets
20 tablets
30 tablets
60 tablets
90 tablets
100 tablets
120 tablets

### 5. Method and route of administration

For oral use.

Read the package leaflet before use.

### 6. Special warning that the medicinal product must be stored out of the reach and sight of children

Keep out of the reach and sight of children.

### 7. Other special warning(s), if necessary

### 8. Expiry date

EXP: MM/YYYY

### 9. Special storage conditions

No special storage conditions

**10. Special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate**

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

**11. Name and address of the marketing authorisation holder.**

Chanelle Medical, Loughrea, Co. Galway, Ireland.

**12. Marketing Authorisation No.:**

PL 13931/0064

**13. Manufacturer's batch number**

<Batch> <Lot> <BN> {number}

**14. General classification for supply**

Medicinal product subject to medical prescription

**15. Instructions on use**

**16. Instructions in Braille**

Exemin 25 mg film-coated tablets

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**{NATURE/TYPE}**

**1. NAME OF THE MEDICINAL PRODUCT**

Exemin 25 mg film-coated tablets
Exemestane

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Chanelle Medical

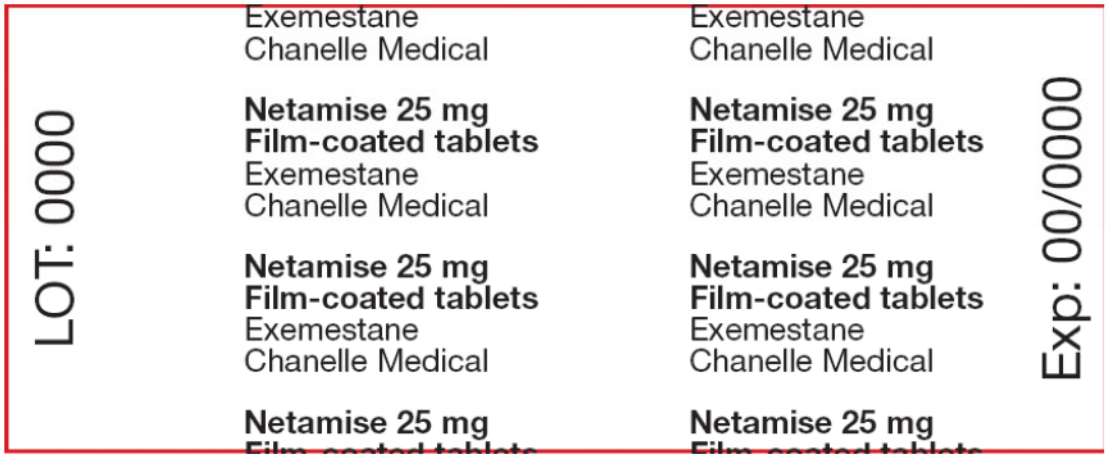
**3. EXPIRY DATE**

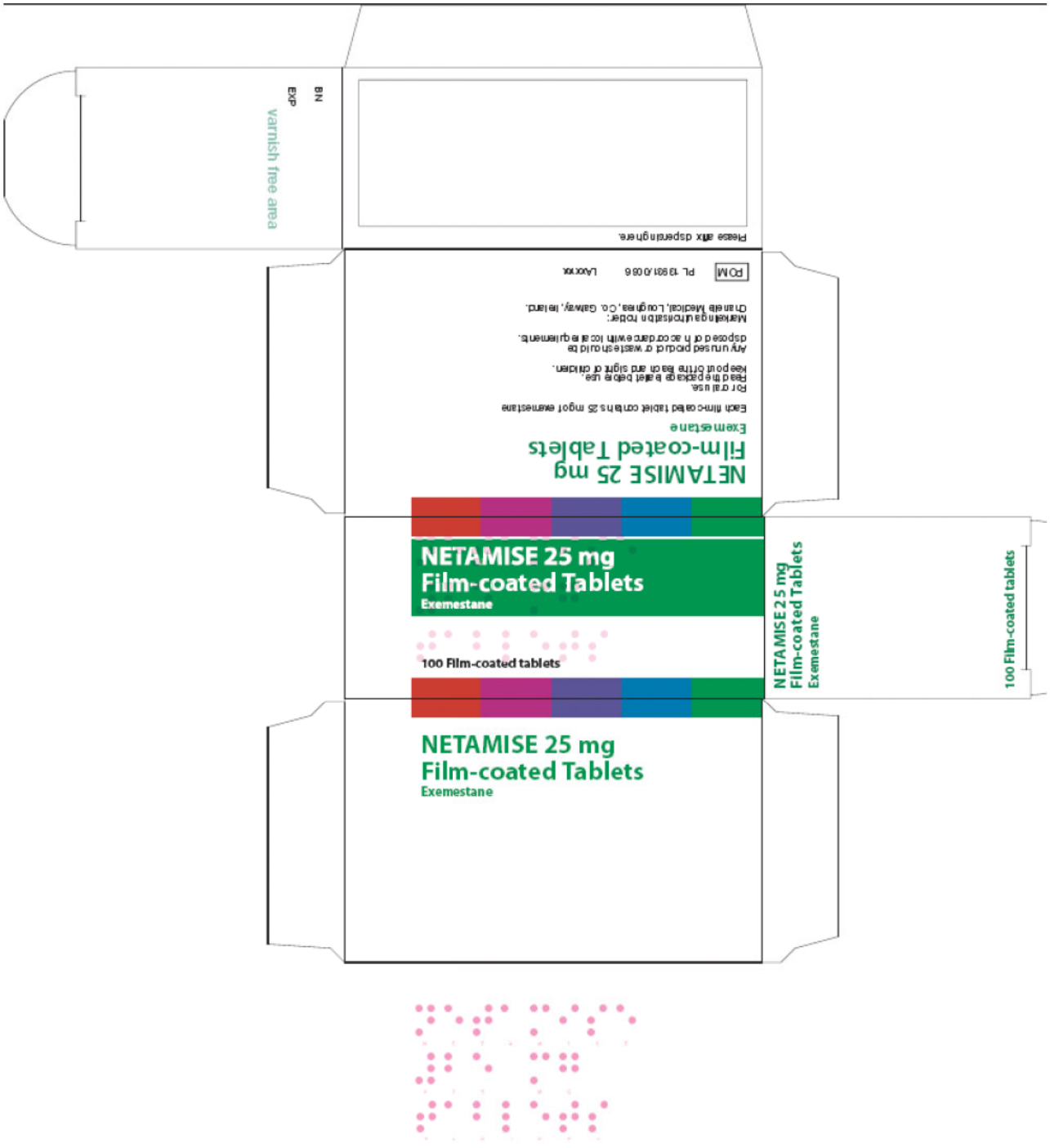
EXP: MM/YYYY

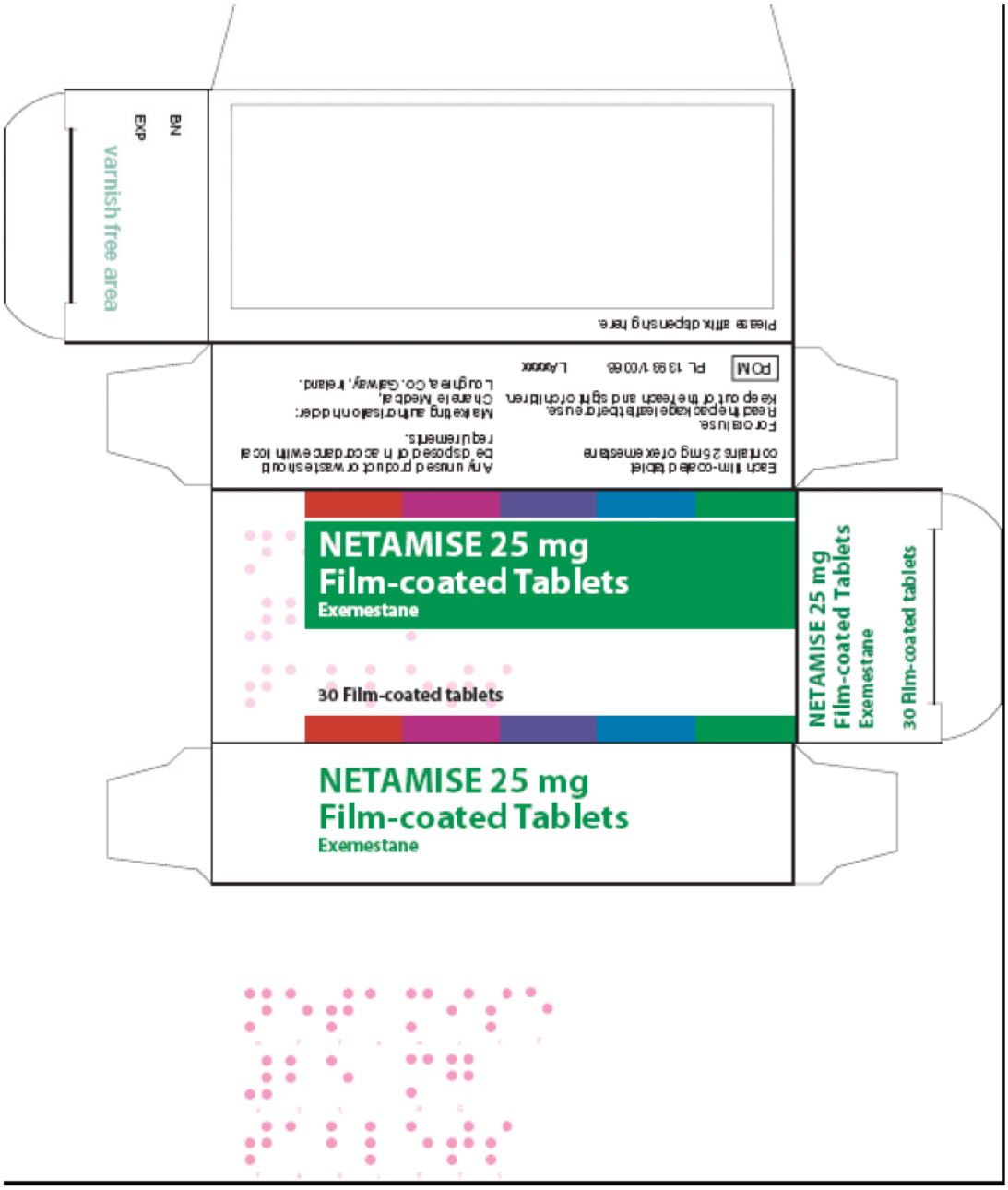
**4. BATCH NUMBER**

Batch :

**5. OTHER**


LOT: 0000
Exemestane
Chanelle Medical
Netamise 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Netamise 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Netamise 25 mg
Exemestane
Chanelle Medical
Netamise 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Netamise 25 mg
Film-coated tablets
Exemestane
Chanelle Medical
Netamise 25 mg
Exp: 00/0000


BN
EXP
varnish free area
Please affix dispensing label.
PL 13931/0086 LAXXXXX
PoM
Marketing authorisation holder:
Chanelle Medical, Loughrea, Co. Galway, Ireland.
Any unused product or waste should be disposed of in accordance with local requirements.
Keep out of the sight and reach of children.
Read the package leaflet before use.
For oral use.
Each film-coated tablet contains 25 mg of exemestane
Exemestane
NETAMISE 25 mg Film-coated Tablets
NETAMISE 25 mg Film-coated Tablets
Exemestane
100 Film-coated tablets
NETAMISE 25 mg Film-coated Tablets
Exemestane
100 Film-coated tablets
NETAMISE 25 mg Film-coated Tablets
Exemestane


varnish free area
EXP
BN
Please affix dispensing here.
POM
PL 1393/0068
LAxxxxx
Each film-coated tablet contains 25mg of exemestane
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Any unused product or waste should be disposed of in accordance with local requirements.
Marketing authorisation holder:
Chanelle Medical,
Loughrea, Co. Galway, Ireland.
NETAMISE 25 mg
Film-coated Tablets
Exemestane
30 Film-coated tablets
NETAMISE 25 mg
Film-coated Tablets
Exemestane
30 film-coated tablets
NETAMISE 25 mg
Film-coated Tablets
Exemestane

# Module 5
# Scientific discussion during initial procedure

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets in the treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy and for advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy, could be approved.

These applications were submitted under Article 10.1, claiming to be generic medicinal products of Aromasin 25mg Film-coated Tablets (PL 00032/0236), which was first licensed to Pharmacia Ltd, UK, on 16th December 1998.

With the UK as the RMS in these Decentralised Procedures (UK/H/2363, 3910-1& 3915/01/DC), Chanelle Medical applied for the Marketing Authorisations for Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets in the following CMSs.

UK/H/236301/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherlands, Poland, Portugal, Romania
UK/H/3910/01/DC - Cyprus, Germany, Spain, France, Hungary, Italy, Malta, Poland, Portugal, Romania
UK/H/3911/01DC - Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, The Netherland, Norway, Poland, Portugal, Romania, Sweden, Slovak Republic
UK/H/3915/01/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherland, Portugal

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, exemestane p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

No new preclinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant a licence for the above products at the end of procedure (Day 210 – 24th November 2010). After subsequent national phase, the UK granted a licence for these products on 18th February 2011 (PL 13931/0062, 64-6).

## II. ABOUT THE PRODUCT

| | |
|---|---|
| Name of the product in the Reference Member State | Exemestane/Xatane/Netamise/Exemin 25mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Exemestane |
| Pharmacotherapeutic classification (ATC code) | L02BG06 |
| Pharmaceutical form and strength(s) | Film-coated Tablets, 25mg |
| Reference numbers for the Decentralised Procedures | UK/H/2363, 3910-1&3915/01/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | UK/H/236301/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherlands, Poland, Portugal, Romania<br>UK/H/3910/01/DC - Cyprus, Germany, Spain, France, Hungary, Italy, Malta, Poland, Portugal, Romania<br>UK/H/3911/01DC - Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, The Netherland, Norway, Poland, Portugal, Romania, Sweden, Slovak Republic<br>UK/H/3915/01/DC - Belgium, Czech Republic, Germany, Spain, France, Hungary, Italy, The Netherland, Portugal |
| Marketing Authorisation Number(s) | PL 13931/0062, 64-6 |
| Name and address of the authorisation holder | Chanelle Medical<br>Dublin Road<br>Loughrea<br>County Galway<br>Ireland |

# III SCIENTIFIC OVERVIEW AND DISCUSSION

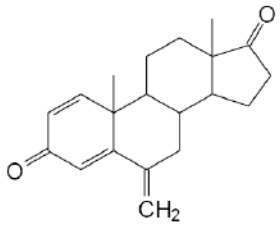
## III.1 QUALITY ASPECTS

### DRUG SUBSTANCE

INN: Exemestane

Chemical Name: 6-Methyleneandrosta-1, 4-diene-3,17-dione10, 13-dimethyl-6-methylidene-7,8,9,10,11,12,13,14,15,16-decahydrocyclopenta[a] phenanthrene – 3,17-dione

Structure:




Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.4

Appearance: white to slightly yellow crystalline powder. It is freely soluble in N,N-dimethylformamide and soluble in methanol. Exemestane is insoluble in water.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

### DRUG PRODUCT

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients silica, colloidal anhydrous, crospovidone, hypromellose 5cP, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, sodium starch glycolate (Type A) and Film coating (hypromellose 5cP, macrogol, talc and titanium dioxide (E171)).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

It had been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were suitably provided. This is acceptable.

**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Aromasin 25mg Film-coated Tablets.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future production full-scale batches.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in white PVC/PVDC – aluminium blisters. Pack sizes are 14, 15, 20, 30, 60, 90, 100 and 120 Tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with no storage condition has been set.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The Marketing Authorisation Holder has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical point of view.

## III.2 PRE-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of exemestane are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of these type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

## III.3 CLINICAL ASPECTS
**Clinical Pharmacology**
***Pharmacokinetics***
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

**Study 1**
A single centre randomized, open label, two period, crossover bioequivalence study of Exemestane 25mg Film-coated Tablets (test) and Aromasin 25mg Film-coated Tablets (reference) in healthy female adults was performed under fed conditions.

**Results**
**Summary of Statistical Analysis of Plasma Exemestane Pharmacokinetics Variables**

| Variable (unit) | LSMean | | Mean Ratio (%) | 90% Confidence Interval of Ratio (%) | Intra-individual CV (%) |
|---|---|---|---|---|---|
| | Exemestane (test) | Aromasin ™ (Reference) | | | |
| $C_{max}$ (ng/ml) | 21.432 | 23.530 | 91.08 | 82.38 – 100.70 | 39.0 |
| AUC $_{(0\text{-tlast})}$ (h.ng/mL) | 78.963 | 82.292 | 95.96 | 93.18 – 98.81 | 11.0 |
| AUC $_{(0\text{-inf})}$ (h.ng/mL | 84.187 | 87.587 | 96.12 | 93.49 – 98.82 | 10.4 |
| $T_{1/2}$ (h) | 15.882 | 15.870 | 100.07 | 94.56 – 105.91 | 21.5 |
| $T_{max}$ (h) | 1.333 | 1.000 | p-value: 0.2041 | | |

The 90% confidence intervals for $C_{max}$ and AUC were within the pre-defined limits (80-125%). Bioequivalence has been demonstrated between the test and reference formulations.

***Pharmacodynamics***
No new data have been submitted and none are required for these generic applications.

***Clinical Efficacy***
No new data have been submitted and none are required.

***Clinical Safety***
No new data have been submitted and none are required.

***Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling***
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

***Clinical Expert Report***
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

***Marketing Authorisation Application (MAA) Forms***
The MAA forms are medically satisfactory.

***Clinical Conclusion***
There are no objections to the approval of these products from a clinical point of view.

## IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

### QUALITY

The important quality characteristics of Exemestane/Xatane/Netamise/Exemin 25mg Film-coated 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 have been demonstrated between the applicant's Exemestane 25mg Film-coated Tablets and the reference product, Aromasin 25mg Film-coated Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

### RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with exemestane is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |