Exemestane 25 mg film-coated tablets

PL 24668/0260

UKPAR

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EXEMESTANE 25 MG FILM-COADED TABLETS

PL 24668/0260

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Exemestane 25 mg film-coated tablets (Product Licence number: PL 24668/0260) on 11 January 2011.

Exemestane belongs to a group of medicines called aromatase inhibitors. This means that it interferes with some of the actions of aromatase, which is needed to make the female sex hormone oestrogen, especially in post-menopausal women. Reducing oestrogen levels in the body is a way of treating hormone dependent breast cancer. Exemestane is used to treat hormone dependent 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 has not worked well enough.

Exemestane 25 mg film-coated tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
EXEMESTANE 25 MG FILM-COATED TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted a Marketing Authorisation for the medicinal product Exemestane 25 mg film-coated tablets to Caduceus Pharma Ltd. on 11 January 2011. This medicine is only available on prescription.

Exemestane tablets are used in the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy. They are also used in 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.

This application is submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that Exemestane 25 mg film-coated tablets is a generic version of Aromasin 25mg film coated tablets, which is currently licensed to Pharmacia Limited (PL 00032/0236). This reference product has been authorised in the EEA for over 10 years (since 16 Dec 1998), the legal basis of this application is, therefore, acceptable and the ten year rule is complied with.

Assurance has been provided that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

No new preclinical studies were conducted, which is acceptable given that the application is for a generic version of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application is for a generic version of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: EXEMESTANE

rINN: Exemestane
Chemical name: 6-Methyleneandrosta-1,4-diene-3,17-dione
CAS No.: 107868-30-4
Structure:

![Molecule structure](image)

Molecular formula: $C_{20}H_{24}O_2$
Relative molecular mass: 296.4

Manufacture
Synthesis of the drug substance from the designated starting materials 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.

Control
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Container closure system
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Stability
Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT: EXEMESTANE 25 MG FILM-COATED TABLETS
Exemestane 25 mg film-coated tablets contain the pharmaceutical excipients povidone K30, StarCap 1500 co-processed starch excipient (maize starch (bleached) and partially pregelatinised starch), sodium starch glycolate (type A), cellulose microcrystalline type 101, talc, colloidal anhydrous silica, magnesium stearate,
polysorbate 80 and Opadry II (polyvinyl alcohol-partly hydrolyzed, titanium dioxide (E171), macrogol 3350 and talc).

All excipients comply with the specifications in their respective European Pharmacopoeia monographs, with the exception of StarCap 1500 co-processed starch excipient and Opadry II. However, the components of these excipients comply with the requirements of the European Pharmacopoeia monographs and/or the United States Pharmacopeia/National Formulary. In the absence of a European Pharmacopoeia monograph for StarCap 1500 co-processed starch excipient and Opadry II, this is acceptable. Satisfactory certificates of analysis have been provided for all excipients.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to formulate a robust, stable, solid oral dosage form equivalent to the reference product, Aromasin 25mg film coated tablets and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

Suitable pharmaceutical development data have been provided for this application. The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed product can be considered a generic version of Aromasin 25mg film coated tablets.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container closure system**

The tablets are sealed in blisters of clear PVC film and heat sealable aluminium blister foil. The finished product is available in packs of 10, 30, 40, 60, 90 or 100 film-coated 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 18 months has been set for the product when it is stored in the original packaging.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. The bio-analytical methods used have been satisfactorily validated. Bioequivalence has been demonstrated between the test and reference products.

Expert report
A satisfactory expert report is provided from an appropriately qualified author.

Product literature
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along 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.

Pharmaceutical conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of exemestane are well-known, no further preclinical studies are required and none have been provided.

The applicant’s preclinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

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

There are no objections to the approval of this product from a preclinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics

In support of this application a bioequivalence study comparing the test and reference products was performed.

Methods

The study was a randomised, open-label, 2-way crossover bioavailability study in 66 healthy, adult, post menopausal or sterilised (for at least 3 months prior to first dose) female volunteers under fed conditions.

On the mornings of day 1 of each period for each group subjects received a single oral 25 mg exemestane dose with water. Doses were separated by a 21 day wash out period. Subjects were housed in the clinic from at least 10 hours before dosing until after the 24 hour post dose events. They then returned for at intervals up to 96 hour post dose. Food was restricted overnight for at least 10 hours before dosing until 30 minutes prior to dosing time.

At this time subjects were given a standard non high fat breakfast to be entirely consumed in 30 minutes. Subjects were fasted for at least 4 hours following dosing. Water was not permitted from 1 hour before dosing to 1 hour after dosing but was allowed at other times. Standard meals were provided at 4 and 9 hours after dosing and at appropriate times thereafter. During housing, post-dose meal plans were identical in both periods. All 66 subjects satisfied the inclusion and exclusion criteria at check-in. Blood samples were taken as predose and at intervals up to 96 hours post dose.

Bioanalytical methods have been described and validated satisfactorily.

The pharmacokinetic and statistical analysis was performed using ANOVA on ln-transformed AUC₀₋₉, AUC₀₋inf, and C₉. The ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC₀₋₉, AUC₀₋inf and C₉. The statistical analysis was done using the SAS GLM procedure. Non parametric analysis of T₉ was performed using methods of Koche and Hauske. A sample size of 66 subjects was calculated using a power of at least 85% and an alpha error of 5%. The power was defined as the probability of having a 90% confidence interval for a test/reference ratio within the acceptance criteria of 0.8-1.25. A true ratio between 0.95-1.05 and an intra-subject CV of 36% were used.

All pharmacokinetic methods are considered adequate.

Results

Out of a total of 66 female subjects enrolled in the study, 62 subjects completed the clinical phase. One subject was withdrawn as they vomited 25 minutes post-dose in period 1; another was withdrawn as the subject consumed antibiotics during the washout period prior to check in at period 2; another was withdrawn prior to dosing in period 2 due to adverse events and another was withdrawn due to adverse events. There were no non-zero pre-dose concentrations reported. BLQ values were set to zero for the pharmacokinetic and statistical analyses.
The protocol deviations can be considered as minor and are not judged to affect the pharmacokinetic conclusions of the study. No non-zero pre-dose concentrations were reported, indicating an adequate washout period.

### Results of main pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exemestane</th>
<th>Aromasin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>$11.8989_{\pm}5.54869$</td>
<td>$13.4839_{\pm}6.02093$</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng-h/ml)</td>
<td>$42.06_{\pm}16.076$</td>
<td>$42.95_{\pm}14.012$</td>
</tr>
<tr>
<td>$AUC_{0-inf}$ (ng-h/ml)</td>
<td>$45.05_{\pm}16.940$</td>
<td>$46.90_{\pm}14.670$</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>$1.8633_{\pm}0.86142$</td>
<td>$1.5201_{\pm}0.90092$</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>$13.89$</td>
<td>$14.37$</td>
</tr>
<tr>
<td>$K_{el}$ (l/h)</td>
<td>0.066</td>
<td>0.063</td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the test to reference product for ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{\text{max}}$ are within the accepted range of 80-125%, in line with CPMP/EWP/QWP/1401/98 Note for guidance on the investigation of bioavailability and bioequivalence.

### Pharmacokinetic conclusion

Based on the submitted bioequivalence study the applicant’s Exemestane 25 mg film-coated tablets is considered bioequivalent to Aromasin 25mg film coated tablets.

### Efficacy

No new data on the efficacy of this product have been submitted and none are required for this type of application.

### Safety

No new or unexpected safety issues were raised by the bioequivalence study.

### Product literature

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

### Pharmacovigilance system

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.

**Risk management plan (RMP)**
The applicant has not submitted an RMP, nor is one needed for an application of this kind.

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

**Conclusion**
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Exemestane 25 mg 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 risk-benefit balance.

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

EFFICACY
The efficacy of exemestane is well established. Bioequivalence has been demonstrated between the applicant’s product and the reference product.

SAFETY
No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with exemestane is considered to have demonstrated the therapeutic value of the compound. The risk: benefit ratio is, therefore, considered to be acceptable for this product and a Marketing Authorisation may be granted.
**EXEMESTANE 25 MG FILM-COATED TABLETS**

**PL 24668/0260**

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 23 June 2009</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA</td>
</tr>
<tr>
<td></td>
<td>considered the application valid on 30 June 2009</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further</td>
</tr>
<tr>
<td></td>
<td>information relating to the clinical dossier on 29 September 2009 and the</td>
</tr>
<tr>
<td></td>
<td>quality dossier on 13 November 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information</td>
</tr>
<tr>
<td></td>
<td>on the clinical and quality dossiers on 16 June 2010</td>
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<td>5</td>
<td>Following assessment of the response the MHRA requested further information</td>
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<td>relating to the quality dossier on 3 August 2010</td>
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<td>6</td>
<td>The applicant responded to the MHRA’s request, providing further information</td>
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<tr>
<td></td>
<td>on the quality dossier on 24 August 2010</td>
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<tr>
<td>7</td>
<td>The application was determined on 11 January 2011</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Exemestane 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.

Exemestane 25 mg film-coated tablets are white, round, lenticular, with uniform appearance and intact edges.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy.

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
Adult and elderly patients
The recommended dose of exemestane is one 25 mg tablet to be taken once daily, 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 section 5.2).

Children
Exemestane is not recommended for use in children.
4.3 **Contraindications**
Known hypersensitivity to the active substance or to any of the excipients. Premenopausal women, pregnant or lactating 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 section 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 600 mg daily and a single dose of exemestane 25 mg, the AUC of exemestane was reduced by 54% and $C_{\text{max}}$ 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**

It is not known whether exemestane is excreted into human milk. Exemestane should not be administered to lactating woman.

**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 section 4.3 and section 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 (e.g. 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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

**Nervous system disorders:**

- **Very common** Headache
- **Common** Dizziness, carpal tunnel syndrome
- **Uncommon** Somnolence

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

**Metabolism and nutrition disorders:**
*Common* Anorexia

**Vascular disorders:**
*Very common* Hot flushes

**General disorders and administration site conditions:**
*Very common* Fatigue
*Common* Pain, peripheral oedema
*Uncommon* Asthenia

**Psychiatric disorders:**
*Very common* Insomnia
*Common* Depression

**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.

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

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 always 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/m² 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: steroidal aromatase inhibitor; anti-neoplastic agent.
ATC code: 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 of 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:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Exemestane Population Events /N (%)</th>
<th>Tamoxifen Events /N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>354 /2352 (15.1%)</td>
<td>453 /2372 (19.1%)</td>
<td>0.76 (0.67-0.88)</td>
<td>0.00015</td>
</tr>
<tr>
<td>ER+ patients</td>
<td>289 /2023 (14.3%)</td>
<td>370 /2021 (18.3%)</td>
<td>0.75 (0.65-0.88)</td>
<td>0.00030</td>
</tr>
<tr>
<td><strong>Contralateral breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>20 /2352 (0.9%)</td>
<td>35 /2372 (1.5%)</td>
<td>0.57 (0.33-0.99)</td>
<td>0.04158</td>
</tr>
<tr>
<td>ER+ patients</td>
<td>18 /2023 (0.9%)</td>
<td>33 /2021 (1.6%)</td>
<td>0.54 (0.30-0.95)</td>
<td>0.03048</td>
</tr>
<tr>
<td><strong>Breast cancer free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>289 /2352 (12.3%)</td>
<td>373 /2372 (15.7%)</td>
<td>0.76 (0.65-0.89)</td>
<td>0.00041</td>
</tr>
<tr>
<td>ER+ patients</td>
<td>232 /2023 (11.5%)</td>
<td>305 /2021 (15.1%)</td>
<td>0.73 (0.62-0.87)</td>
<td>0.00038</td>
</tr>
<tr>
<td><strong>Distant recurrence free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>248 /2352</td>
<td>297 /2372</td>
<td>0.83 (0.70-0.97)</td>
<td>0.02621</td>
</tr>
<tr>
<td></td>
<td>(10.5%)</td>
<td>(12.5%)</td>
<td>0.98</td>
<td></td>
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</tr>
<tr>
<td>ER+ patients</td>
<td>194 /2023 (9.6%)</td>
<td>242 /2021 (12.0%)</td>
<td>0.78 (0.65-(0.95))</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>0.01123</td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival** \(^d\)

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>222 /2352 (9.4%)</td>
<td>262 /2372 (11.0%)</td>
<td>0.85 (0.71-(1.02))</td>
</tr>
<tr>
<td>ER+ patients</td>
<td>178 /2023 (8.8%)</td>
<td>211 /2021 (10.4%)</td>
<td>0.84 (0.68-(1.02))</td>
</tr>
<tr>
<td>* Log-rank test; ER+ patients = oestrogen receptor positive patients;</td>
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<td></td>
</tr>
</tbody>
</table>

\(^a\) 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 20,000 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 14C-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 (CLcr < 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:*
Povidone K30
Maize starch (bleached)
Starch, pregelatinised (partially)
Sodium starch glycolate, type A
Cellulose microcrystalline type 101
Talc
Silica, colloidal anhydrous
Magnesium stearate
Polysorbate 80

*Film-coating:*
Polyvinyl alcohol-partly hydrolyzed
Titanium dioxide (E171)
Macrogol 3350
Talc
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Al/PVC blister: 18 months.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Al/PVC blister.

Pack sizes:
Blister: 10, 30, 40, 60, 90 and 100 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street, London W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0260

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/01/2011

10 DATE OF REVISION OF THE TEXT
11/01/2011
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 pharmacist.

In this leaflet:
1 What Exemestane is and what it is used for
2 Before you take Exemestane
3 How to take Exemestane
4 Possible side effects
5 How to store Exemestane
6 Further information

1 What Exemestane is and what it is used for
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 allergic (hypersensitive) to exemestane (the active ingredient in Exemestane tablets) or to any of the other ingredients of Exemestane tablets. 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.

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 tablets 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
Exemestane tablets are not suitable for use in children.

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),
- the herbal remedy St John’s Wort (Hypericum perforatum), or preparations containing it.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Do not take Exemestane if you are pregnant or breast-feeding.
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 dizzy, sleepy or weak whilst taking Exemestane, you should not attempt to drive or operate machinery.
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 have any further questions on the use of this product, ask your doctor or pharmacist.

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 (nausea)
- 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, carpel 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 gets serious or if you notice any side effect not listed on this leaflet, please tell your doctor or your pharmacist as soon as possible.

How to store Exemestane
Keep out of the reach and sight of children.
Store in the original package.
Do not use Exemestane tablets after the expiry date which is stated on the carton and blister pack (EXP). The expiry date refers to the last day of that month.
Medicines 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.

Further information
What Exemestane tablets contain
- The active substance is exemestane.
- Each film-coated tablet contains 25 mg exemestane.
- The other ingredients are: crospovidone K30, maize starch (bleached), starch pregelatinized (partially), sodium starch glycolate type A, cellulose microcrystalline type 101, talc, silica colloidal anhydrous, magnesium stearate and polysorbate 80; film-coating: polyvinyl alcohol partially hydrolyzed, talc, macrogol 3550 and titanium dioxide (E171).

What Exemestane tablets looks like and contents of the pack
Exemestane 25 mg film-coated tablets are white, round, biconvex, with uniform appearance and intact edges.

Pack sizes
Blisters packs: 10, 30, 40, 60, 90 and 100 film coated tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Cadusus Pharma Ltd., 6th Floor, 94 Wigmore Street, London W1U 3RF, United Kingdom
Manufacturer: S.C. Sandan Pharma S.R.L., 11th Ion Mihalache Blvd., 011171, Bucharest, Romania

This leaflet was last updated in August 2010.
LABELLING

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Exemestane 25 mg film-coated tablets
Exemestane

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Ltd.

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Lot:

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON (BLISTERS)

1. NAME OF THE MEDICINAL PRODUCT

Exemestane 25 mg film-coated tablets
Exemestane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg exemestane.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>tablets</td>
</tr>
<tr>
<td>30</td>
<td>tablets</td>
</tr>
<tr>
<td>40</td>
<td>tablets</td>
</tr>
<tr>
<td>60</td>
<td>tablets</td>
</tr>
<tr>
<td>90</td>
<td>tablets</td>
</tr>
<tr>
<td>100</td>
<td>tablets</td>
</tr>
</tbody>
</table>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

9. SPECIAL STORAGE CONDITIONS

Store in the original package.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street, London W1U 3RF
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0260

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

(exemestane 25 mg film-coated tablets)

16. INFORMATION IN BRAILLE

(exemestane 25 mg film-coated tablets)