

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

**PT. PFIZER INDONESIA**  
Local Product Document

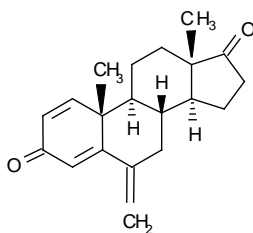
Generic Name: Exemestane tablets  
Trade Name: Aromasin®  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017

## 1. NAME OF THE MEDICINAL PRODUCT

Aromasin®

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet for oral administration contains 25 mg of exemestane, which is an irreversible, steroidal aromatase inactivator. Exemestane is chemically described as 6-methylenandrosta-1,4-diene-3,17-dione. Its molecular formula is  $C_{20}H_{24}O_2$  and its structural formula is as follows:



The active ingredient is a white to slightly yellow crystalline powder with a molecular weight of 296.41. Exemestane is freely soluble in N,N-dimethylformamide, soluble in methanol and practically insoluble in water.

For the full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Sugar-coated tablet.

Round, biconvex, off-white to slightly greyish sugar-coated tablets, about 6 mm diameter printed with numbers 7663 on one side in black ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Exemestane is indicated for the treatment of advanced breast cancer in women with natural or induced post-menopausal status whose disease has progressed following anti-oestrogen therapy. Patient selection should be based on positive oestrogen and/or progesterone receptor status, because efficacy has not been demonstrated when it is absent.

Exemestane is indicated for the adjuvant treatment of post-menopausal women with estrogen-receptor positive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy.

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

## **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, preferably after a meal.

In patients with advanced breast cancer, treatment with exemestane should continue until tumor progression is evident.

In patients with early breast cancer, treatment with exemestane should continue until completion of five years of adjuvant endocrine therapy, or until local or distant recurrence or new contralateral breast cancer.

### Hepatic or Renal Insufficiency

No dose adjustments are required for patients with hepatic or renal insufficiency.

### Children

Not recommended for use in children.

## **4.3 Contraindications**

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

## **4.4 Special warnings and special 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.

As exemestane is a potent estrogen lowering agent, reductions in bone mineral density can be anticipated. 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. Patients treated with exemestane should be carefully monitored and treatment for osteoporosis should be initiated as appropriate.

Routine assessment of 25 hydroxy vitamin D levels prior to the start of aromatase inhibitor treatment should be considered, due to the high prevalence of severe deficiency associated in women with early breast cancer (EBC). Women with Vitamin D deficiency should receive supplementation with Vitamin D.

## **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 aldo-keto reductases and does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, the specific inhibition of CYP3A4 by ketoconazole showed no significant effects on the pharmacokinetics of exemestane.

Although administration of rifampicin, a potent CYP3A4 inducer, significantly decreased exemestane systemic exposure ( $C_{max}$  and AUC), the suppression of plasma estrogen levels (estrone sulfate) produced by exemestane was not influenced. Therefore, exemestane can be

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

given concomitantly with inducers of CYP3A4 without dosage adjustment.

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 co-administered with oestrogen-containing medicines as these would negate its pharmacological action.

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  $C_{max}$  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 Aromasin.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

No clinical data on exposed pregnancies are available with exemestane. Studies on animals have shown reproductive toxicity. 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 women who are lactating.

#### **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**

##### Clinical Trials:

Exemestane was generally well tolerated across all studies and in the clinical studies, conducted with exemestane 25 mg/day, adverse events were usually mild to moderate.

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

The discontinuation 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 flush (14%) and nausea (12%).

Most adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (e.g., hot flush).

Drug-related adverse events that occurred during clinical trials are listed below. Data from post-marketing surveillance are also included. The reported adverse reactions are listed below within each MedDRA System Organ Class (SOC) by decreasing order of medical seriousness.

Generic Name: Exemestane tablets  
 Trade Name: Aromasin  
 CDS Effective Date: June 03, 2021  
 Supersedes: September 07, 2017  
 Approved by BPOM:

**Table 1. Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC**

<b>System Organ Class</b>	<b>Very Common ≥ 1/10</b>	<b>Common ≥1/100 to &lt; 1/10</b>	<b>Uncommon ≥ 1/1,000 to &lt; 1/100</b>	<b>Rare ≥ 1/10,000 to &lt; 1/1,000</b>
Immune system disorders			Hypersensitivity*	
Metabolism and nutrition disorders		Anorexia		
Psychiatric disorders	Depression Insomnia			
Nervous system disorders	Headache Dizziness	Paraesthesia* Carpal tunnel syndrome	Somnolence	
Vascular disorders	Hot flush			
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Constipation Diarrhoea Dyspepsia		
Hepatobiliary disorders				Hepatitis* <sup>§</sup> Hepatitis cholestatic* <sup>§</sup>
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash Pruritus* Alopecia Urticaria*		Acute generalised exanthematous pustulosis* <sup>§</sup>
Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain <sup>a</sup>	Fracture Osteoporosis	Trigger finger*	Tenosynovitis stenans* <sup>§</sup>
General disorders and administration site conditions	Fatigue Pain	Oedema peripheral		
Investigations	Blood alkaline phosphatase increased Hepatic enzyme increased Blood bilirubin increased			

Generic Name: Exemestane tablets  
 Trade Name: Aromasin  
 CDS Effective Date: June 03, 2021  
 Supersedes: September 07, 2017  
 Approved by BPOM:

<b>System Organ Class</b>	<b>Very Common ≥ 1/10</b>	<b>Common ≥1/100 to &lt; 1/10</b>	<b>Uncommon ≥ 1/1,000 to &lt; 1/100</b>	<b>Rare ≥ 1/10,000 to &lt; 1/1,000</b>
* Adverse Drug Reaction (ADR) identified post-marketing. § ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3". <sup>a</sup> Includes: arthralgia, and less frequently pain in limb, osteoarthritis, back pain, arthritis, myalgia and joint stiffness.				

In patients with advanced breast cancer, 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. Thrombocytopenia and leucopenia have been occasionally reported.

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

In the early breast cancer trial, gastric ulcer was observed at a slightly higher frequency in the exemestane arm compared to tamoxifen (0.7% vs. <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.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: [pv-center@pom.go.id](mailto:pv-center@pom.go.id)

Phone: +62-21-4244691 Ext.1079

Website: <https://e-meso.pom.go.id/ADR>

PT Pfizer Indonesia

Email: [IDN.AEReporting@pfizer.com](mailto:IDN.AEReporting@pfizer.com)

Website: [www.pfizersafetyreporting.com](http://www.pfizersafetyreporting.com)

#### **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 post-menopausal 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<sup>2</sup> basis. There is no specific antidote to overdose and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

observation of the patient, is indicated.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: steroidal aromatase inhibitor; anti-neoplastic agent.

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 post-menopausal women. In post-menopausal women, orally administered exemestane significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In post-menopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

In the randomised peer reviewed controlled clinical trial, Aromasin<sup>®</sup> 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 post-menopausal 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.

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. These findings indicate that glucocorticoid or mineralocorticoid replacements are not warranted.

A slight non-dose-dependent increase in serum LH and FSH levels has been observed even at low doses. However, this pharmacological class effect is expected and probably results from feedback at the pituitary level due to the reduction in estrogen levels that stimulate the pituitary secretion of gonadotropins (also in post-menopausal women).

### Clinical Studies

#### Treatment of Advanced Breast Cancer

In a randomized peer reviewed controlled clinical trial, exemestane at the daily dose of 25 mg 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 post-menopausal 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.

#### Adjuvant Treatment of Early Breast Cancer

In a multicenter, randomized, double-blind study (Intergroup Exemestane Study [IES]), conducted in 4724 postmenopausal patients with estrogen-receptor-positive or unknown primary breast cancer, patients who had remained disease-free after receiving adjuvant tamoxifen therapy for 2 to 3 years, were randomized to receive 3 to 2 years of exemestane

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

(25 mg/day) or tamoxifen (20 or 30 mg/day) to complete a total of 5 years of hormonal therapy.

#### *35-Month Median Follow-up (Primary efficacy analysis)*

After a median duration of therapy of about 27 months and a median follow-up of about 35 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 over the observed study period exemestane reduced the risk of breast cancer recurrence by 31% compared with tamoxifen (hazard ratio 0.69;  $p=0.00003$ ). 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 0.32,  $p=0.0034$ ) and significantly prolonged breast cancer free survival (hazard ratio 0.65,  $p<0.00001$ ) and distant recurrence free survival (hazard ratio 0.70,  $p=0.00083$ ).

At the time of analysis, overall survival was not significantly different in the two groups with 116 deaths occurring in the exemestane group and 137 in the tamoxifen group (hazard ratio 0.86,  $p=0.23$ ).

Preliminary results from an endometrial sub-study indicate that after 2 years of treatment there was a median decrease in endometrial thickness of 28.6% in the exemestane-treated patients compared to an increase of 5.3% in the tamoxifen-treated patients. Endometrial thickening, reported at the start of study treatment, was reversed to normal for 50% of patients treated with exemestane.

#### *52-Month Median Follow-up*

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 DFS compared with continuation of tamoxifen therapy. Analysis showed that over 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 risk of contralateral breast cancer (hazard ratio 0.57,  $p = 0.04158$ ), significantly prolonged breast cancer-free survival (hazard ratio 0.76,  $p = 0.00041$ ), and distant recurrence-free survival (hazard ratio 0.83,  $p = 0.02621$ ).

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. However, for the subset of patients with estrogen 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.

In the whole study population, a statistically significant 23% reduction in the risk of dying

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

(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).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients compared with tamoxifen only-treated patients (3.6% vs. 5.3%).

Results from an endometrial sub-study 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 for 54% of patients treated with exemestane.

#### *87-Month Median Follow-up*

After a median duration of therapy of about 30 months and a median follow-up of about 87 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 DFS compared with continuation of tamoxifen therapy. Analysis showed that over the observed study period exemestane reduced the risk of breast cancer recurrence by 16% compared with tamoxifen (hazard ratio 0.84,  $p = 0.002$ ). The beneficial effect of exemestane over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Exemestane also significantly prolonged breast cancer-free survival (hazard ratio 0.82,  $p = 0.00263$ ), and distant recurrence-free survival (hazard ratio 0.85,  $p = 0.02425$ ). Exemestane also reduced risk of contralateral breast cancer; however, the effect was no longer statistically significant (hazard ratio 0.74,  $p = 0.12983$ ). In the whole study population, a trend for improved overall survival was observed for exemestane (373 deaths) compared to tamoxifen (420 deaths) with a hazard ratio 0.89 (log rank test:  $p = 0.08972$ ), representing an 11% reduction in the risk of death in favor of exemestane. However, for the subset of patients with estrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.86 (log-rank test:  $p = 0.04262$ ), representing a clinically and statistically significant 14% reduction in the risk of dying.

In the whole study population, a statistically significant 18% reduction in the risk of dying (hazard ratio for overall survival 0.82; Wald chi square test:  $p = 0.0082$ ) 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).

#### *119-Month Final Follow-up*

After a median duration of therapy of about 30 months and a median follow-up of about 119 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 DFS compared with continuation of tamoxifen therapy. Analysis showed that over the observed study period exemestane reduced the risk of breast cancer recurrence by 14% compared with tamoxifen (hazard ratio 0.86,  $p = 0.00393$ ). The beneficial effect of exemestane over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

Exemestane also significantly prolonged breast cancer-free survival (hazard ratio 0.83,  $p < 0.00152$ ), and distant recurrence-free survival (hazard ratio 0.86,  $p = 0.02213$ ). Exemestane also reduced risk of contralateral breast cancer; however, the effect was no longer statistically significant (hazard ratio 0.75,  $p = 0.10707$ ).

In the whole study population, overall survival was not statistically different between the two groups with 467 deaths (19.9%) occurring in the exemestane group and 510 deaths (21.5%) in the tamoxifen group (hazard ratio 0.91,  $p = 0.15737$ , not adjusted for multiple testing). For the subset of patients with estrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.89 (log-rank test:  $p = 0.07881$ ) in the risk of dying in the exemestane group relative to the tamoxifen group.

In the whole study population, a statistically significant 14% reduction in the risk of dying (hazard ratio for OS 0.86; Wald chi square test:  $p = 0.0257$ ) was observed for exemestane compared with tamoxifen when adjusting for the pre specified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients compared with tamoxifen only-treated patients (9.9% vs. 12.4%).

## **5.2 Pharmacokinetic properties**

### Absorption

After oral administration of Exemestane tablets, the drug 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.

Exemestane pharmacokinetics are linear time independent and do not demonstrate unexpected accumulation with repeated administration. The terminal elimination half-life of exemestane is approximately 24 h. Concomitant administration with food increases exemestane bioavailability by approximately 40%.

### Distribution

The volume of distribution of exemestane, not corrected for the oral bioavailability (V/F), is ca 20.000 L. 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 metabolized by oxidation of the methylene moiety on the 6 position by CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldo-keto reductase followed by conjugation. The clearance of exemestane not corrected for the oral bioavailability (CL/F) is ca 500 L/h. Exemestane metabolites are either inactive or demonstrate markedly lower aromatase inhibition than the parent compound. Following the administration of a  $^{14}\text{C}$ -labeled exemestane dose, approximately equal amounts (ca 40%) of drug-derived radioactivity were eliminated in urine and feces within 1 week. Between 0.1% to 1% of the radioactive dose was excreted in the urine as unchanged  $^{14}\text{C}$ -labeled exemestane.

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

### Special populations

#### Age:

No significant correlation between exemestane systemic exposure and the age of subjects have been observed.

#### Renal insufficiency:

In patients with severe renal impairment ( $CL_{cr} < 30$  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**

### Acute toxicity

The acute oral toxicity of exemestane is low with  $LD_{50}$  in rodents  $>2000$  mg/kg and the compound was well tolerated in dogs up to 1000 mg/kg.

### Chronic toxicity

In repeated-dose toxicity studies, the no-toxic-effect levels after 1 year's treatment were 50 mg/kg/day in rats and 30 mg/kg/day in dogs, which yielded systemic exposure approximately 3 to 6 times higher compared to the exposure in humans at 25 mg/day. In all species tested and in both sexes, there were effects on reproductive and accessory organs which were related to the pharmacological activity of exemestane. 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

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

effects is considered to be clinically relevant to the treatment of patients with exemestane.

#### Reproductive toxicity

In animal reproduction studies in rats and rabbits, exemestane was embryotoxic, fetotoxic, and abortifacient. When rats were administered exemestane from 14 days prior to mating until either days 15 or 20 of gestation, and resuming for the 21 days of lactation, an increase in placental weight was seen at 4 mg/kg/day (approximately 1.5 times the recommended human daily dose on a mg/m<sup>2</sup> basis). Increased resorptions, reduced number of live fetuses, decreased fetal weight, retarded ossification, prolonged gestation and abnormal or difficult labor was observed at doses equal to or greater than 20 mg/kg/day (approximately 7.5 times the recommended human daily dose on a mg/m<sup>2</sup> basis). Daily doses of exemestane given to rabbits during organogenesis caused a decrease in placental weight at 90 mg/kg/day (approximately 70 times the recommended human daily dose on a mg/m<sup>2</sup> basis) and, in the presence of maternal toxicity, abortions, an increase in resorptions, and a reduction in fetal body weight were seen at 270 mg/kg/day (approximately 210 times the recommended human dose on a mg/m<sup>2</sup> basis). No malformations were noted when exemestane was administered to pregnant rats or rabbits during the organogenesis period at doses up to 810 and 270 mg/kg/day, respectively (approximately 320 and 210 times the recommended human dose on a mg/m<sup>2</sup> basis, respectively).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tablet core: Colloidal hydrated silica, Crospovidone, Hypromellose, Magnesium carbonate light, Magnesium stearate, Mannitol, Microcrystalline cellulose, Methyl p-hydroxybenzoate, Macrogol 6000, Polysorbate 80, Polyvinyl alcohol, Simethicone emulsion, Sodium starch glycollate, Sucrose, Titanium dioxide.

Sugar-coating: Hypromellose; Polyvinylalcohol; Simeticone; Macrogol; Sucrose; Magnesium carbonate, light; Titanium dioxide; Methyl parahydroxybenzoate; Cetyl esters wax; Talc; Carnauba wax.

Printing ink: Ethyl alcohol; Shellac; Iron oxides, Titanium oxide.

### **6.2 Nature and contents of container**

Aromasin<sup>®</sup> is packaged in carton containing 2 blisters @ 15 sugar-coated tablets.  
Registration No.: DK10254200316A1

### **6.3 Special precautions for storage**

Store below 30°C.

### **6.4 Special precautions for disposal and other handling**

Keep out of reach of children.

## **HARUS DENGAN RESEP DOKTER**

### **Manufactured by:**

Pfizer Italia S.r.l.,  
Ascoli, Italy

Generic Name: Exemestane tablets  
Trade Name: Aromasin  
CDS Effective Date: June 03, 2021  
Supersedes: September 07, 2017  
Approved by BPOM:

**Imported by:**  
PT Pfizer Indonesia  
Jakarta Indonesia

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

## **Leaflet kemasan: Informasi bagi pengguna**

### **Aromasin® 25 mg tablet salut gula Eksemestan**

**Baca semua bagian leaflet ini dengan cermat sebelum mulai menggunakan obat ini karena berisi informasi penting bagi Anda.**

- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 12.

#### **Isi leaflet ini:**

1. Nama produk
2. Deskripsi produk
3. Apa kandungan obat ini?
4. Kekuatan obat
5. Apa kegunaan obat ini?
6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?
7. Kapan seharusnya Anda tidak menggunakan obat ini?
8. Apa yang harus dipertimbangkan saat meminum obat ini?
9. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?
10. Apakah obat tersebut aman bagi ibu hamil dan menyusui?
11. Apakah pasien diizinkan mengemudi dan mengoperasikan mesin saat menggunakan obat ini?
12. Apa saja potensi efek yang tidak diinginkan dari penggunaan obat ini?
13. Tanda-tanda dan gejala-gejala overdosis
14. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?
15. Bagaimana cara menyimpan obat ini?
16. Nomor Otorisasi Pemasaran
17. Nama produsen/importir/Pemegang Hak Pemasaran
18. Tanggal revisi
19. Peringatan khusus

#### **1. Nama produk**

Aromasin®

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

## 2. Deskripsi produk

Aromasin® tablet salut gula berbentuk bulat, bikonveks, berwarna putih pucat hingga agak keabu-abuan, berdiameter sekitar 6 mm, bertuliskan 7663 pada satu sisi dengan tinta hitam. Untuk administrasi oral yang mengandung 25 mg eksemestan, merupakan inaktivator aromatase steroid yang ireversibel. Bahan aktif ini berupa serbuk kristalin berwarna putih hingga agak kuning dengan berat molekul 296,41. Eksemestan terlarut secara bebas dalam N, N-dimetilformamid, larut dalam metanol dan praktis tidak larut dalam air.

## 3. Apa kandungan obat ini?

Tablet Aromasin® untuk administrasi oral yang mengandung 25 mg eksemestan.

### Daftar excipien

Inti tablet: Silika terhidrasi koloid, Krosповidon, Hipromelos, Magnesium karbonat ringan, Magnesium stearat, Manitol, Mikrokristalin selulosa, Metil p-hidroksibenzoat, Makrogol 6000, Polisorbat 80, Polivinil alkohol, Emulsi simetikon, Natrium pati glikolat, Sukrosa, Titanium dioksida.

Salut gula: Hipromelosa; Polivinil alkohol; Simetikon; Makrogol; Sukrosa; Magnesium karbonat, ringan; Titanium dioksida; Metil parahidroksibenzoat; Lilin setil ester; Talk; Lilin karnauba.

Tinta cetak: Etil alkohol; Syelak; Besi oksida, Titanium oksida.

## 4. Kekuatan obat

25 mg

## 5. Apa kegunaan obat ini?

Eksemestan diindikasikan untuk mengobati kanker payudara stadium lanjut pada perempuan dengan status pascamenopause alami atau terinduksi yang penyakitnya mengalami perburukan setelah menjalani terapi antiestrogen. Pilihan pasien harus didasarkan pada status reseptor estrogen dan/atau progesteron positif, karena efikasi belum ditunjukkan tanpa adanya reseptor tersebut.

Eksemestan diindikasikan sebagai terapi ajuvan pada perempuan pascamenopause yang menderita kanker payudara stadium awal dengan reseptor estrogen positif, setelah menjalani terapi tamoksifen ajuvan awal selama 2–3 tahun.

## 6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

### **Orang dewasa dan pasien lansia**

Selalu gunakan obat ini sesuai dengan petunjuk dokter Anda. Tanyakan kepada dokter jika Anda merasa tidak yakin.

Tablet Aromasin® hanya boleh diberikan secara oral setelah makan sekitar waktu yang sama setiap hari. Dokter Anda akan memberi tahu Anda cara meminum Aromasin® dan untuk berapa lama.

Dosis yang dianjurkan adalah satu tablet 25 mg setiap hari.

Jika Anda perlu datang ke rumah sakit selama meminum Aromasin®, beri tahu staf medis mengenai pengobatan yang sedang Anda lakukan.

### **Penggunaan pada anak-anak**

Aromasin® tidak cocok untuk digunakan pada anak-anak.

### **Jika Anda lupa meminum Aromasin®**

Jangan meminum dosis ganda untuk mengganti tablet yang terlewatkan.

Jika Anda lupa untuk meminum tablet Anda, minum sesegera mungkin setelah Anda ingat. Jika sudah mendekati waktu untuk dosis berikutnya, minumlah pada waktu yang semestinya.

### **Jika Anda berhenti meminum Aromasin®**

Jangan berhenti meminum tablet Anda sekali pun Anda sudah merasa sehat, kecuali jika dokter Anda memerintahkan demikian.

Jika Anda memiliki pertanyaan lebih lanjut mengenai kegunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

## **7. Kapan seharusnya Anda tidak menggunakan obat ini?**

### **Jangan meminum Aromasin®:**

- jika Anda mengalami atau sebelumnya pernah mengalami alergi terhadap eksemestan (bahan aktif dalam Aromasin®) atau bahan lain dalam obat ini.
- jika Anda belum pernah melewati “menopause”, yaitu Anda masih mengalami menstruasi setiap bulan.
- jika Anda sedang hamil, ada kemungkinan hamil, atau sedang menyusui.

### **Aromasin® mengandung sukrosa, natrium, dan metil parahidroksibenzoat**

- Jika Anda telah diberi tahu oleh dokter bahwa Anda memiliki intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum meminum produk medisinal ini.
- Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, sehingga pada dasarnya bisa dikatakan ‘bebas natrium’.

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

- Aromasin® mengandung sejumlah kecil metil parahidroksibenzoat, yang dapat menyebabkan reaksi alergi (kemungkinan terjadi belakangan), jika hal ini terjadi silakan hubungi dokter Anda.

## 8. Apa yang harus dipertimbangkan saat meminum obat ini?

### Peringatan dan tindakan pencegahan

- Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Aromasin®.
- Sebelum menjalani pengobatan dengan Aromasin®, dokter Anda mungkin akan mengambil sampel darah untuk memastikan Anda telah mencapai menopause.
- Pemeriksaan rutin terhadap kadar vitamin D Anda juga akan dilakukan sebelum pengobatan, karena bisa saja kadarnya sangat rendah pada tahap awal kanker payudara. Anda akan diberi suplemen vitamin D jika kadar Anda di bawah normal.
- Sebelum meminum Aromasin®, beri tahu dokter Anda jika Anda mengalami gangguan hati atau ginjal.
- Beri tahu dokter Anda jika Anda memiliki riwayat atau sedang mengalami kondisi mana pun yang memengaruhi kekuatan tulang Anda. Dokter Anda mungkin akan mengukur kepadatan tulang Anda sebelum dan selama pengobatan dengan Aromasin®. Ini dilakukan karena obat-obatan dari golongan ini dapat menurunkan kadar hormon perempuan dan hal ini dapat menyebabkan hilangnya kandungan mineral pada tulang, sehingga dapat menurunkan kekuatannya.

## 9. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter atau apoteker jika Anda meminum, baru saja meminum, atau mungkin meminum obat-obatan lain, termasuk obat-obatan yang diperoleh tanpa resep.

Aromasin® tidak boleh diberikan secara bersamaan dengan obat yang mengandung estrogen.

Obat-obatan berikut ini harus digunakan dengan hati-hati selama meminum Aromasin®. Beri tahu dokter Anda jika Anda sedang meminum obat-obatan seperti:

- rifampisin (golongan antibiotik),
- karbamazepin atau fenitoin (antikejang yang digunakan untuk mengobati epilepsi),
- obat herbal St John's Wort (*Hypericum perforatum*), atau sediaan yang mengandung obat herbal tersebut.

## 10. Apakah obat tersebut aman bagi ibu hamil dan menyusui?

- Jangan meminum Aromasin® jika Anda sedang hamil atau menyusui.
- Jika Anda sedang hamil atau kemungkinan hamil, laporkan kepada dokter Anda.
- Diskusikan penggunaan alat kontrasepsi dengan dokter jika ada kemungkinan bahwa Anda bisa hamil.

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

## **11. Apakah pasien diizinkan mengemudi dan mengoperasikan mesin saat menggunakan obat ini?**

Jika Anda merasa mengantuk, pusing, atau lemah selama meminum Aromasin®, Anda tidak boleh mencoba untuk mengemudi atau mengoperasikan mesin.

## **12. Apa saja potensi efek yang tidak diinginkan dari penggunaan obat ini?**

Seperti semua obat-obatan yang ada, obat ini bisa menimbulkan efek samping, meskipun tidak semua orang mengalaminya. Hipersensitivitas, peradangan organ hati (hepatitis), dan peradangan saluran empedu pada organ hati yang mungkin menyebabkan terjadinya kulit menguning (hepatitis kolestatik). Gejalanya antara lain merasa tidak enak badan, mual, sakit kuning (menguningnya kulit dan mata), gatal-gatal, nyeri perut di sebelah kanan, dan hilangnya selera makan. Hubungi dokter Anda segera untuk mendapatkan saran medis mendesak jika Anda mengalami gejala mana pun.

Secara umum, Aromasin® dapat ditoleransi dengan baik dan efek samping berikut ini yang teramati pada pasien yang diterapi dengan Aromasin® pada dasarnya bersifat ringan atau sedang. Sebagian besar efek samping dikaitkan dengan menurunnya estrogen (misalnya sensasi rasa panas akibat menopause (hot flushes)).

### **Sangat umum: dapat dialami lebih dari 1 di antara 10 orang**

- Depresi
- Sulit tidur
- Sakit kepala
- Sensasi panas
- Pusing
- Merasa mual
- Peningkatan keringat
- Nyeri otot dan sendi (termasuk osteoarthritis, sakit punggung, arthritis, dan kaku pada persendian)
- Kelelahan
- Nyeri perut
- Peningkatan kadar enzim hati
- Peningkatan kadar penguraian hemoglobin dalam darah
- Peningkatan kadar enzim darah dalam darah akibat kerusakan hati
- Nyeri

### **Umum: dapat dialami hingga 1 di antara 10 orang**

- Kehilangan selera makan
- Sindrom terowongan karpal (kombinasi antara kesemutan, kebas, dan nyeri yang dialami seluruh bagian tangan kecuali jari kelingking) atau rasa kesemutan pada kulit
- Muntah, konstipasi, gangguan pencernaan, diare
- Kerontokan rambut

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

- Ruam kulit, kaligata, dan gatal-gatal
- Penipisan tulang yang dapat menurunkan kekuatannya (osteoporosis) dapat menyebabkan patah tulang (patah atau retak) dalam beberapa kasus
- Tangan dan kaki membengkak
- Merasa lemah

**Tidak umum: dapat dialami hingga 1 di antara 100 orang**

- Hipersensitivitas
- Mengantuk
- *Trigger finger* (meningkatnya kekakuan pada jari-jemari, jari-jemari terkunci dan menetap pada tempatnya)

**Jarang: dapat dialami hingga 1 di antara 1.000 orang**

- Munculnya lepuh-lepuh kecil pada area kulit dalam bentuk ruam
- Peradangan organ hati
- Peradangan saluran empedu pada organ hati yang menyebabkan kulit menguning
- Peradangan selubung yang membungkus tendon tangan

**Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia**

- Rendahnya kadar sel darah putih tertentu dalam darah
- Penurunan jumlah sel darah putih
- Penurunan jumlah trombosit dalam darah

Perubahan jumlah sel darah tertentu (limfosit) dan trombosit yang beredar dalam darah Anda, khususnya pada pasien yang sebelumnya menderita limfopenia (penurunan limfosit dalam darah) juga mungkin teramati.

**Melaporkan efek samping**

Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda bisa membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

Untuk melaporkan efek samping, kunjungi [www.pfizersafetyreporting.com](http://www.pfizersafetyreporting.com) atau kirimkan email ke [IDN.AEReporting@pfizer.com](mailto:IDN.AEReporting@pfizer.com).

Nama Generik: Eksemestan  
Nama Dagang: Aromasin®  
Tanggal Berlaku CDS: 3 Juni 2021  
Menggantikan: Tidak Ada  
Disetujui oleh BPOM:

### **13. Tanda-tanda dan gejala-gejala overdosis**

Efek samping mana pun yang disebutkan di atas mungkin terjadi.

### **14. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?**

Jika tanpa sengaja meminum terlalu banyak tablet, hubungi segera dokter Anda atau kunjungi langsung unit gawat darurat di rumah sakit terdekat. Tunjukkan kepada mereka kemasan tablet Aromasin®.

### **15. Bagaimana cara menyimpan obat ini?**

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah melewati tanggal kedaluwarsa yang tertera pada kemasan luarnya dan blister setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada tanggal terakhir di bulan tersebut.
- Simpan obat pada suhu dibawah 30°C

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker mengenai cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

### **16. Nomor Otorisasi Pemasaran**

Aromasin® dikemas dalam dus berisi 2 blister @ 15 tablet salut gula.  
No. Registrasi: DKI0254200316A1

### **17. Nama produsen/importir/Pemegang Hak Pemasaran**

#### **Diproduksi oleh:**

Pfizer Italia S.r.l.,  
Ascoli, Italy

#### **Diimpor oleh:**

PT Pfizer Indonesia  
Jakarta Indonesia

### **18. Tanggal revisi**

08/2025

### **19. Peringatan khusus**

**HARUS DENGAN RESEP DOKTER**