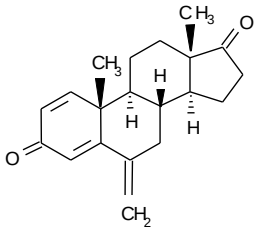
PT. PFIZER INDONESIA
Local Product Document

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.

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 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.

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

System Organ Class	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
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*§ Hepatitis cholestatic*§
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash Pruritus* Alopecia Urticaria*		Acute generalised exanthematous pustulosis*§
Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain[a]	Fracture Osteoporosis	Trigger finger*	Tenosynovitis stenosans*§
General disorders and administration site conditions	Fatigue Pain	Oedema peripheral		
Investigations	Blood alkaline phosphatase increased Hepatic enzyme increased Blood bilirubin increased			

*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".
[a] 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
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: 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^2 basis. There is no specific antidote to overdosage and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: 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® 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 (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 (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.

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}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}C-labeled exemestane.

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 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^2 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^2 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^2 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^2 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^2 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® is packaged in carton containing 2 blisters @ 15 sugar-coated tablets.
Registration No.: DKI0254200316A1

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

Imported by:
PT Pfizer Indonesia
Jakarta Indonesia