

1. Name of the Medicinal Product

Aromasin.

2. Qualitative and Quantitative Composition

Each sugar-coated tablet contains 25 mg exemestane.

3. Pharmaceutical Form

Coated tablets.

3.1 Description

Sugar-coated tablets for oral administration.

Aromasin tablets are 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 adjuvant treatment of post-menopausal women with estrogen receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to Exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy.

Exemestane is indicated for the second-line treatment of advanced breast cancer (ABC) in women with natural or induced post-menopausal status whose disease has progressed following anti-estrogen therapy alone.

Exemestane is also indicated for the third-line treatment in post-menopausal woman with ABC whose disease has progressed following multiple hormonal therapies. Efficacy has not been demonstrated in patients with estrogen 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, preferably after a meal.

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.

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

Hepatic or Renal Insufficiency

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

4.3 Contraindications

Hypersensitivity

Exemestane is contraindicated in patients with a known hypersensitivity to the drug or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Because of its mode of action, exemestane should not be administered to women with pre-menopausal endocrine status.

Exemestane should not be co-administered with estrogen-containing products as these would negate its pharmacological action.

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 metabolized through cytochrome P450 (CYP) 3A4 and aldoketoreductases 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 pharmacokinetic effects were observed in a pharmacokinetic interaction study with rifampicin, a potent CYP3A4 inducer, the pharmacologic activity (i.e., estrogen suppression) was not affected, and a dosage adjustment is not required.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Exemestane is contraindicated in women who are or may become pregnant, because it may cause harm to the fetus. Studies in animals have shown reproductive toxicity (See section 5.3).

Lactation

It is not known whether exemestane is excreted into human milk. Exemestane should not be used in women who are lactating.

4.7 Effects on Ability to Drive and Use Machines

The effect of exemestane on the ability to drive and use machinery has not been systematically evaluated.

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 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 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

System Organ Class	Adverse Drug Reactions
Immune system disorders	Hypersensitivity*
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Depression Insomnia
Nervous system disorders	Headache Dizziness Carpal tunnel syndrome Paraesthesia*
Vascular disorders	Hot flush
Gastrointestinal disorders	Abdominal pain Nausea Vomiting Diarrhoea

Table 1. Adverse Drug Reactions

System Organ Class	Adverse Drug Reactions
	Constipation Dyspepsia
Hepatobiliary disorders	Hepatitis* Hepatitis cholestatic*
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis* Rash Hyperhidrosis Alopecia Urticaria* Pruritus*
Musculoskeletal and connective tissue disorders	Fracture Osteoporosis Joint and musculoskeletal pain ^a Trigger finger* Tendon disorders including tendon rupture, tendonitis and tenosynovitis*
General disorders and administration site conditions	Pain Fatigue Oedema peripheral
Investigations	Hepatic enzyme increased Blood bilirubin increased Blood alkaline phosphatase increased

(*) Adverse Drug Reaction (ADR) identified post-marketing.

(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.

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.

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. In rats and dogs, lethality was observed after single oral doses equivalent to 2000 and 4000 times, respectively, the recommended human dose on a mg/m² basis. There is no specific antidote to overdose and treatment must be symptomatic.

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, estrogens are produced primarily from the conversion of androgens into estrogens through the aromatase enzyme in peripheral tissues. Estrogen 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 estrogen 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%.

Exemestane does not possess any progestogenic or estrogenic 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

Adjuvant Treatment of Early Breast Cancer

In a multicenter, randomized, double-blind study (Intergroup Exemestane Study [IES]), conducted in 4724 post-menopausal 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, $p = 0.23$).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients versus tamoxifen-treated patients (2.2% vs. 3.5%).

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).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients compared with tamoxifen only-treated patients (5.6% vs. 7.6%).

Results from a bone sub-study indicate that treatment with exemestane for 2 to 3 years following 3 to 2 years of tamoxifen treatment increased bone loss while on treatment (mean % change from baseline for BMD at 36 months: -3.37 [spine], -2.96 [total hip] for exemestane and -1.29 [spine], -2.02 [total hip] for tamoxifen). However, by the end of the follow-up period there were minimal differences between the treatment arms in the change in BMD from baseline, with the tamoxifen arm having slightly greater final reductions in BMD at all sites (mean % change from baseline for BMD at 24 months post-treatment -2.17 [spine], -3.06 [total hip] for exemestane and -3.44 [spine], -4.15 [total hip] for tamoxifen).

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 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%).

Treatment of Advanced Breast Cancer

In a phase 3 study conducted by the EORTC (European Organization for Research and Treatment of Cancer), exemestane was compared to tamoxifen as first-line treatment of advanced breast cancer. Results indicated that patients in the exemestane treatment group had a longer median Progression Free Survival (PFS) time compared to tamoxifen (9.9 months vs. 5.8 months) with a hazard ratio of 0.84 in favor of exemestane ($p = 0.028$ by Wilcoxon test; $p = 0.121$ by log-rank test). Exemestane-treated patients also had a higher objective tumor response rate compared to tamoxifen (44% vs. 31%).

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.

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 17 ng/mL are reached by 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.

Metabolism and Excretion

Exemestane is metabolized via oxidation of the methylene moiety on the 6 position by CYP3A4 and/or reduction of the 17-keto group by aldoketoreductase 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 ¹⁴C-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 ¹⁴C-labeled exemestane.

Special populations

Age

No significant correlation between exemestane systemic exposure and age has 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 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 necessary.

5.3 Preclinical Safety Data

Acute toxicity

The acute oral toxicity of exemestane is low with LD₅₀ 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.

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/m² 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/m² 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/m² 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/m² 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/m² basis, respectively).

6. Pharmaceutical Particulars

6.1 List of Excipients

Mannitol, Hypromellose, Magnesium stearate, Silica colloidal hydrated, Croscopovidone,

Sodium starch glycolate (type A), Polysorbate 80, Microcrystalline cellulose, Purified water.

Coating agents: Hypromellose, Simethicone emulsion, Macrogols, Sucrose, Magnesium carbonate light, Titanium dioxide (E171), Methyl p-hydroxybenzoate, Polyvinyl alcohol.

6.2 Shelf Life

See shelf life on outer carton.

6.3 Special Precautions for Storage

Store below 30°C.

6.4 Nature and Content of Container

Aromasin tablets are presented in aluminium foil/PVC-PVDC foil blister strips in cartons containing 30 or 90 capsules.

Some product strengths or pack size may not be available in your country.

7. Manufactured by

Pfizer Italia S.r.l.
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63100 Ascoli Piceno (AP)
Italy

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