AROMASTAN
F.C. TABLET 25MG

1. NAME OF THE MEDICINAL PRODUCT

AROMASTAN F.C. TABLET 25MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg exemestane.
For List of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets

White, round, biconvex film-coated tablets, with uniform appearance and intact edges.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

Exemestane is indicated for the treatment of advanced breast cancer in women with natural or induced post-menopausal status whose disease has progressed following anti- estrogen 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 early breast cancer, treatment with exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by exemestane), or earlier if tumor relapse occurs.

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.

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.

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. Therefore, whenever clinically appropriate, the post-menopausal status should be ascertained by assessment of LH, FSH and estradiol levels.

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

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

As exemestane is a potent estrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of exemestane on long-term fracture risk remains undetermined. During adjuvant treatment with exemestane, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of bone mineral density loss caused by exemestane are not available, treatment of osteoporosis should be initiated as appropriate. Patients treated with exemestane should be carefully monitored.

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.

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

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

4.6. Pregnancy and Lactation

Pregnancy

Women should not use exemestane during pregnancy 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

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

The 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 flushes (14%) and nausea (12%).

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

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1,000).

Metabolism and nutrition disorders:	
Common	Anorexia
Psychiatric disorders:	
Very common	Depression, insomnia
Nervous system disorders:	
Very common	Headache, dizziness
Common	Carpal tunnel syndrome
Uncommon	Somnolence
Vascular disorders:	
Very common	Hot flushes
Gastrointestinal disorders:	
Very common	Abdominal pain, nausea
Common	Vomiting, diarrhea, constipation, dyspepsia
Hepatobiliary disorders:	
Very common	Hepatic enzyme increased, blood bilirubin increased, blood alkaline phosphatase increased
Skin and subcutaneous tissue disorders:	
Very common	Increased sweating
Common	Alopecia, rash
Musculoskeletal and bone disorders:	
Very common	Joint and musculoskeletal pain (*)
Common	Fracture, osteoporosis
General disorders and administration site conditions:	
Very common	Pain, fatigue
Common	Edema peripheral
Uncommon	Asthenia

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

In patients with advanced breast cancer, thrombocytopenia and leucopenia have been rarely reported. An occasional decrease in lymphocytes has been observed in approximately 20% of patients receiving exemestane, particularly in patients with pre-existing lymphopenia. However, mean lymphocyte values in these patients did not change significantly over time and no corresponding increase in viral infections was observed. These effects have not been observed in patients treated in early breast cancer studies.

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.

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

Adverse events and illnesses	Exemestane (N = 2252)	Tamoxifen (N = 2279)
Hot flushes	488 (21.7%)	456 (20.0%)
Fatigue	372 (16.5%)	345 (15.1%)
Headache	303 (13.5%)	255 (11.2%)
Insomnia	279 (12.4%)	199 (8.7%)
Sweating increased	270 (12.0%)	242 (10.6%)
Dizziness	225 (10.0%)	197 (8.6%)
Nausea	199 (8.8%)	205 (9.0%)
Osteoporosis	116 (5.2%)	65 (2.9%)
Vaginal haemorrhage	87 (3.9%)	109 (4.8%)
Gynecological	81 (3.6%)	154 (6.8%)
Other primary cancer	56 (2.5%)	84 (3.7%)
Vomiting	51 (2.3%)	52 (2.3%)
Visual disturbance	44 (2.0%)	48 (2.1%)
Cardiovascular disorder	21 (0.9%)	39 (1.7%)
Osteoporotic fracture	17 (0.8%)	13 (0.6%)
Thromboembolism	15 (0.7%)	40 (1.8%)
Myocardial infarction	14 (0.6%)	4 (0.2%)

Post-marketing Experience:

Immune system disorders
Uncommon: Hypersensitivity

Nervous system disorders
Common: Paresthesia

Hepatobiliary disorders
Rare: Hepatitis, hepatitis cholestatic

Skin and subcutaneous tissue disorders
Common: Urticaria, pruritus
Rare: Acute generalized exanthematous pustulosis

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 2,000 and 4,000 times, respectively, the recommended human dose on a mg/m^2 basis. There is no specific antidote to overdosage and treatment must be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: steroidal aromatase inhibitor, anti-neoplastic agent ATC: L02BG06.

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 nondose-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

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).

52-month main efficacy results in all patients (intention-to-treat population) and estrogen receptor-positive patients are summarized in the table below:

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

Overall survival[d]				
All patients	**222**/2352 (9.4%)	**262**/2372 (11.0%)	0.85 (0.71-1.02)	0.07362
ER+ patients	**178**/2023 (8.8%)	**211**/2021 (10.4%)	0.84 (0.68-1.02)	0.07569

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

In the 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 prespecified 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 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 17ng/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 ^{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 age has been observed.

Renal Insufficiency

In patients with severe renal insufficiency (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 LD_{50} in rodents >2,000 mg/kg and the compound was well tolerated in dogs up to 1,000 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. Radioactivity related to ^{14}C-exemestane crossed the placenta of rats following oral administration of 1 mg/kg exemestane. The concentration of exemestane and its metabolites was approximately equivalent in maternal and fetal blood. 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: Povidone K30, StarCap 1500 [Maize starch, Starch, pregelatinized],Sodium starch glycolate, Cellulose microcrystalline type 101, Talc, Silica, colloidal anhydrous, Magnesium stearate, Polysorbate 80

Film-coating: Opadry II 85F18422 White [Polyvinyl alcohol-part. Hydrolyzed, Titanium dioxide (E171), Macrogol 3350, Talc]

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Refer to Expiry Date on outer carton.

6.4 Special Precautions for Storage

Do not store above 30°C.

6.5 Nature and Contents of Container

Blister packs: Box of 3x10's and box of 10x10's

6.6 Instructions for Use/Handling

No special requirements.

7. MANUFACTURER

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