Exemestane Tablets USP 25mg Taj Pharma

1. Name of the medicinal product

Exemestane Tablets USP 25mg Taj Pharma

2. Qualitative and quantitative composition

Each film-coated tablet contains
Exemestane USP 25mg
Excipients: Q.S.
Colour: Titanium Dioxide USP

For a full list of excipients, see Section 6.1.

3. Pharmaceutical form

Film-coated tablet, White opaque
PVC/PVdC-Alu blister

4. Clinical particulars

4.1 Therapeutic indications

Exemestane Taj Pharma is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer (EBC), following 2 – 3 years of initial adjuvant tamoxifen therapy.

Exemestane Taj Pharma is indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy. Efficacy has not been demonstrated in patients with oestrogen receptor negative status.

4.2 Posology and method of administration

Posology

Adult and elderly patients

The recommended dose of Exemestane Taj Pharma is one 25mg tablet to be taken once a daily, preferably after a meal.

In patients with early breast cancer, treatment with Exemestane Taj Pharma should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Exemestane Taj Pharma), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with Exemestane Taj Pharma should continue until tumour progression is evident.

No dose adjustments are required for patients with hepatic or renal insufficiency (see 5.2).

Paediatric population

Not recommended for use in children

4.3 Contraindications

Exemestane Taj Pharma tablets are contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1, in pre-menopausal women and in pregnant or lactating women.

4.4 Special warnings and precautions for use

Exemestane Taj Pharma 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 Taj Pharma should be used with caution in patients with hepatic or renal impairment.

Exemestane Taj Pharma is a potent oestrogen lowering agent, and a reduction in bone mineral density (BMD) and an increased fracture rate has been observed following administration (see section 5.1). At the commencement of adjuvant treatment with Exemestane Taj Pharma, women with osteoporosis or at risk of osteoporosis should treatment baseline bone mineral health assessment, based on current clinical guidelines and practice. Patients with advanced disease should have their bone mineral density assessed on a case-by-case basis. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Exemestane Taj Pharma are not available, patients treated with Exemestane Taj Pharma tablets should be carefully monitored and treatment for, or prophylaxis of, osteoporosis should be initiated in at risk patients.

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 in women with early breast cancer. 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 CYP3A4 and aldoketoreductases (see section 5.2) and does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, the specific inhibition of CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of Exemestane Taj Pharma.

In an interaction study with rifampicin, a potent CYP450 inducer, at a dose of 600mg daily and a single dose of Exemestane Taj Pharma 25mg, the AUC of Exemestane Taj Pharma 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 Taj Pharma.

Exemestane Taj Pharma 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 Taj Pharma with other anticancer drugs.

Exemestane Taj Pharma should not be coadministered with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available with Exemestane Taj Pharma. Studies on animals have shown reproductive toxicity (See section 5.3). Exemestane Taj Pharma is therefore contraindicated in pregnant women.

Breast-feeding

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

Women of perimenopausal status or child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established (see sections 4.3 and 4.4).

4.7 Effects on ability to drive and use machines

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of the drug. Patients should be advised that, if these events occur, their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

4.8 Undesirable effects

Exemestane Taj Pharma was generally well tolerated across all clinical studies conducted with Exemestane Taj Pharma at a standard dose of 25mg/day, and undesirable effects were usually mild to moderate.

The withdrawal rate due to adverse events was 7.4% in patients with early breast cancer receiving adjuvant treatment with Exemestane Taj Pharma following initial adjuvant tamoxifen therapy. The most commonly reported adverse reactions were hot flushes (22%), arthralgia (18%) and fatigue (16%).

The withdrawal rate due to adverse events was 2.8% in the overall patient population with advanced breast cancer. The most commonly reported adverse reactions were hot flushes (14%) and nausea (12%).

Most adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (eg hot flushes).

The reported adverse reactions are listed below by system organ class and by frequency.

The reported adverse reactions from clinical studies and post-marketing experience are listed below by system organ class and by frequency.

Frequencies are defined as: very common (≥1/10) common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Very common	Leucopenia (**)
Common	Thrombocytopenia (**)
Not Known	Lymphocyte count decreased (**)

Immune system disorders

Uncommon	Hypersensitivity

Metabolism and nutrition disorders:

Common	Anorexia

Psychiatric disorders:

Very common	Depression, Insomnia

Nervous system disorders:

Very common	Headache, Dizziness
Common	Carpal tunnel syndrome, paraesthesia
Rare	Somnolence

Vascular disorders:

Very common	Hot flushes

Gastrointestinal disorders:

Very common	Abdominal pain, Nausea
Common	Vomiting, diarrhoea, constipation, dyspepsia

Hepatobiliary disorders

Very common	Hepatic enzyme increased (†), blood bilirubin increased(†), blood alkaline phosphatase increased(†)
Rare	Hepatitis(†), cholestatic hepatitis(†)

Skin and subcutaneous tissue disorders:

Very common	Increased sweating
Common	Alopecia, rash, urticaria, pruritus
Rare	Acute generalised exanthematous pustulosis (†)

Musculoskeletal and bone disorders:

Very common	Joint and musculoskeletal pain (*)
Common	Osteoporosis, fracture

General disorders and administration site conditions:

Very common	Pain, Fatigue
Common	Oedema peripheral oedema, Asthenia

(*) Includes: arthralgia, and less frequently pain in extremity, 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 Taj Pharma, 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.

(†) Frequency calculated by rule of 3/X

The table below presents the frequency of pre-specified adverse events and illnesses in the early breast cancer study Intergroup Exemestane Taj Pharma 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 Taj Pharma (N = 2249)**	**Tamoxifen (N = 2279)**
Hot flushes	491 (21.8%)	457 (20.1%)
Fatigue	367 (16.3%)	344 (15.1%)
Headache	305 (13.6%)	255 (11.2%)
Insomnia	290 (12.9%)	204 (9.0%)
Sweating increased	270 (12.0%)	242 (10.6%)
Gynaecological	235 (10.5%)	340 (14.9%)
Dizziness	224 (10.0%)	200 (8.8%)
Nausea	200 (8.9%)	208 (9.1%)
Osteoporosis	116 (5.2%)	66 (2.9%)
Vaginal haemorrhage	90 (4.0%)	121 (5.3%)
Other primary cancer	84 (3.6%)	125 (5.3%)
Vomiting	50 (2.2%)	54 (2.4%)
Visual disturbance	45 (2.0%)	53 (2.3%)
Thromboembolism	16 (0.7%)	42 (1.8%)
Osteoporotic fracture	14 (0.6%)	12 (0.5%)
Myocardial infarction	13 (0.6%)	4 (0.2%)

In the IES study, the frequency of ischemic cardiac events in the Exemestane Taj Pharma and tamoxifen treatment arms was 4.5% versus 4.2%, respectively. No significant difference was noted for any individual cardiovascular event including hypertension (9.9% versus 8.4%), myocardial infarction (0.6% versus 0.2%) and cardiac failure (1.1% versus 0.7%).

In the IES study, Exemestane Taj Pharma was associated with a greater incidence of hypercholesterolemia compared with tamoxifen (3.7% vs. 2.1%).

In a separate double blinded, randomized study of postmenopausal women with early breast cancer at low risk treated with Exemestane Taj Pharma (N=73) or placebo (N=73) for 24 months , Exemestane Taj Pharma was associated with an average 7-9% mean reduction in plasma HDL-cholesterol, versus a 1% increase on placebo. There was also a 5-6% reduction in apolipoprotein A1 in the Exemestane Taj Pharma group versus 0-2% for placebo. The effect on the other lipid parameters analysed (total cholesterol, LDL cholesterol, triglycerides, apolipoprotein-B and lipoprotein-a) was very similar in the two treatment groups. The clinical significance of these results is unclear.

In the IES study, gastric ulcer was observed at a higher frequency in the Exemestane Taj Pharma arm compared to tamoxifen (0.7% versus <0.1%). The majority of patients on Exemestane Taj Pharma 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.

4.9 Overdose

Clinical trials have been conducted with Exemestane Taj Pharma given up to 800mg in a single dose to healthy female volunteers and up to 600mg daily to postmenopausal women with advanced breast cancer; these dosages were well tolerated. The single dose of Exemestane Taj Pharma 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 amg/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

Mechanism of action

Exemestane Taj Pharma is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, Exemestane Taj Pharma p.o. significantly lowered serum oestrogen concentrations starting from a 5mg dose, reaching maximal suppression (>90%) with a dose of 10-25mg. In postmenopausal breast cancer patients treated with the 25mg daily dose, whole body aromatization was reduced by 98%.

Exemestane Taj Pharma 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 Taj Pharma had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other enzymes involved in the steroidogenic pathway.

Glucocorticoid or mineralocorticoid replacements are therefore not needed. A non dose-dependent slight increase in serum LH and FSH levels has been observed even at low doses: this effect is, however, expected for the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in oestrogen levels that stimulate the pituitary secretion of gonadotropins also in postmenopausal women.

Clinical efficacy and safety

Adjuvant Treatment of Early Breast Cancer

In a multicentre, randomised, double-blind study (IES), conducted in 4724 postmenopausal patients with oestrogen-receptor-positive or unknown primary breast cancer, patients who had remained disease-free after receiving adjuvant tamoxifen therapy for 2 to 3 years were randomised to receive 3 to 2 years of Exemestane Taj Pharma (25mg/day) or tamoxifen (20 or 30mg/day) to complete a total of 5 years of hormonal therapy.

IES 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 Taj Pharma after 2 to 3 years of adjuvant tamoxifen therapy was associated with a clinically and statistically significant improvement in disease-free survival (DFS) compared with continuation of tamoxifen therapy. Analysis showed that in the observed study period Exemestane Taj Pharma reduced the risk of breast cancer recurrence by 24% compared with tamoxifen (hazard ratio 0.76; p=0.00015). The beneficial effect of Exemestane Taj Pharma over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Exemestane Taj Pharma also significantly reduced the risk of contralateral breast cancer (hazard ratio 0.57, p=0.04158).

In the whole study population, a trend for improved overall survival was observed for Exemestane Taj Pharma (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 Taj Pharma. 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 Taj Pharma 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).

52 month main efficacy results in all patients (intention to treat population) and oestrogen receptor positive patients:

Endpoint **Population**	**Exemestane Taj Pharma** **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 = oestrogen 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 additional analysis for the subset of patients with **oestrogen** receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.83 (log-rank test: p = 0.04250), representing a clinically and statistically significant 17% reduction in the risk of dying.

Results from the IES bone substudy demonstrated that women treated with Exemestane Taj Pharma following 2 to 3 years of tamoxifen treatment experienced moderate reduction in bone mineral density. In the overall study, the treatment emergent fracture incidence evaluated during the 30 months treatment period was higher in patients treated with Exemestane Taj Pharma compared with tamoxifen (4.5% and 3.3% correspondingly, p=0.038).

Results from the IES endometrial substudy indicate that after 2 years of treatment there was a median 33% reduction of endometrial thickness in the Exemestane Taj Pharma-treated patients compared with no notable variation in the tamoxifen-treated patients. Endometrial thickening, reported at the start of study treatment, was reversed to normal (< 5 mm) for 54% of patients treated with Exemestane Taj Pharma.

<u>IES 87-month median follow-up</u>

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 Taj Pharma 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. Results showed that in the observed study period Exemestane Taj Pharma significantly reduced the risk of breast

cancer recurrence by 16% compared with tamoxifen (hazard ratio 0.84; p=0.002).

Overall, the beneficial effect of Exemestane Taj Pharma over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy or hormonal therapy. Statistical significance was not maintained in a few sub-groups with small sample sizes. These showed a trend favouring Exemestane Taj Pharma in patients with more than 9 nodes positive, or previous chemotherapy CMF. In patients with nodal status unknown, previous chemotherapy other, as well as unknown/missing status of previous hormonal therapy a non statistically significant trend favouring tamoxifen was observed.

In addition, Exemestane Taj Pharma 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 Taj Pharma also reduced the risk of contralateral breast cancer, although the effect was no longer statistically significant in this observed study period (hazard ratio 0.74, p = 0.12983). In the whole study population, a trend for improved overall survival was observed for Exemestane Taj Pharma (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 favour of Exemestane Taj Pharma. When adjusting for the pre-specified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates), 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 Taj Pharma compared to tamoxifen in the whole study population.

In the additional analysis for the subset of patients with oestrogen 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.

Results from a bone sub-study indicate that treatment with Exemestane Taj Pharma 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 Taj Pharma and -1.29 [spine], -2.02 [total hip], for tamoxifen). However, by the end of the 24 month post treatment period there were minimal differences in the change in BMD from baseline for both treatment groups, 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 Taj Pharma and -3.44 [spine], -4.15 [total hip] for tamoxifen).

The all fractures reported on-treatment and during follow-up was significantly higher in the Exemestane Taj Pharma group than on tamoxifen (169 [7.3%] versus 122 [5.2%]; p = 0.004), but no difference was noted in the number of fractures reported as osteoporotic.

<u>IES 119-month final follow-up</u>

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 Taj Pharma 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 Taj Pharma reduced the risk of breast cancer recurrence by 14% compared with tamoxifen (hazard ratio 0.86, p = 0.00393). The beneficial effect of Exemestane Taj Pharma over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Exemestane Taj Pharma 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 Taj Pharma 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 Taj Pharma 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 oestrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.89 (log-rank test: p = 0.07881) in the Exemestane Taj Pharma 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 Taj Pharma 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 Taj Pharma-treated patients compared with tamoxifen only-treated patients (9.9% versus. 12.4%).

In the main study, which had a median follow-up in all participants of 119 months (0 – 163.94) and median duration of Exemestane Taj Pharma treatment of 30 months (0 – 40.41), the incidence of bone fractures was reported on 169 (7.3%) patients in the Exemestane Taj Pharma group compared with 122 (5.2%) patients in the tamoxifen group (p=0.004).

Efficacy Results From IES in Postmenopausal Women With Early Breast Cancer (ITT)

	No. of Events		**Hazard Ratio**	
	Exemestane Taj Pharma	**Tamoxifen**	**Hazard Ratio**	**p-value**
30-Month Median Treatment and 34.5-Month Median Follow-Up				
Disease-free survival[a]	213	306	0.69 (95% CI: 0.58-0.82)	0.00003
Breast cancer-free survival[b]	171	262	0.65 (95% CI: 0.54-0.79)	<0.00001
Contralateral	8	25	0.32 (95%	0.00340

breast cancer			CI: 0.15-0.72)	
Distant recurrence-free survival[c]	142	204	0.70 (95% CI: 0.56-0.86)	0.00083
Overall survival[d]	116	137	0.86 (95% CI: 0.67-1.10)	0.22962

30-Month Median Treatment and 52-Month Median Follow-Up

Disease-free survival[a]	354	453	0.77 (95% CI: 0.67-0.88)	0.00015
Breast cancer-free survival[b]	289	373	0.76 (95% CI: 0.65-0.89)	0.00041
Contralateral breast cancer	20	35	0.57 (95% CI: 0.33-0.99)	0.04158
Distant recurrence-free survival[c]	248	297	0.83 (95% CI: 0.70-0.98)	0.02621
Overall survival[d]	222	262	0.85 (95% CI: 0.71-1.02)	0.07362

30-Month Median Treatment and 87-Month Median Follow-Up

Disease-free survival[a]	552	641	0.84 (95% CI: 0.75-0.94)	0.002
Breast cancer-free survival[b]	434	513	0.82 (95% CI: 0.72-0.94)	0.00263
Contralateral breast cancer	43	58	0.74 (95% CI: 0.50-1.10)	0.12983
Distant recurrence-free survival[c]	353	409	0.85 ((95 % CI: 0.74-0.98)	0.02425
Overall survival[d]	373	420	0.89 (95% CI: 0.77-1.02)	0.08972

30-Month Median Treatment and 119-Month Median Follow-Up

Disease-free	672	761	0.86 (95%	0.0039

survival[a]			CI: 0.77-0.95)	3
Breast cancer-free survival[b]	517	608	0.83 (95% CI: 0.74-0.93)	0.00152
Contralateral breast cancer	57	75	0.75 (95% CI: 0.53-1.06)	0.10707
Distant recurrence-free survival[c]	411	472	0.86 (95% CI: 0.75-0.98)	0.02213
Overall survivald	467	510	0.91 (95% CI: 0.81-1.04)	0.15737

CI = confidence interval; IES = Intergroup Exemestane Taj Pharma Study; ITT = intention-to-treat.

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.

Treatment of Advanced Breast Cancer

In a randomised peer reviewed controlled clinical trial, Exemestane Taj Pharma at the daily dose of 25mg has demonstrated statistically significant prolongation of survival, Time to Progression (TTP), Time to Treatment Failure (TTF) as compared to a standard hormonal treatment with megestrol acetate in postmenopausal patients with advanced breast cancer that had progressed following, or during, treatment with tamoxifen either as adjuvant therapy or as first-line treatment for advanced disease.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of Exemestane Taj Pharma tablets, Exemestane Taj Pharma 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 25mg, maximum plasma levels of 18 ng/ml are reached after 2 hours. Concomitant intake with food increases the bioavailability by 40%.

Distribution:

The volume of distribution of Exemestane Taj Pharma, not corrected for the oral bioavailability, is ca 20000 l. The kinetics is linear and the terminal elimination half-life is 24 h. Binding to plasma proteins is 90% and is concentration independent. Exemestane Taj Pharma and its metabolites do not bind to red blood cells.

Exemestane Taj Pharma does not accumulate in an unexpected way after repeated dosing.

Elimination:

Exemestane Taj Pharma is metabolised by oxidation of the methylene moiety on the 6 position by CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of Exemestane Taj Pharma is ca 500 l/h, not corrected for the oral bioavailability.

The metabolites are inactive or the inhibition of aromatase is less than the parent compound.

The amount excreted unchanged in urine is 1% of the dose. In urine and faeces equal amounts (40%) of ^{14}C-labeled Exemestane Taj Pharma were eliminated within a week.

Special populations

Age

No significant correlation between the systemic exposure of Exemestane Taj Pharma and the age of subjects has been observed.

Renal impairment

In patients with severe renal impairment (CL_{cr} < 30 ml/min) the systemic exposure to Exemestane Taj Pharma was 2 times higher compared with healthy volunteers.

Given the safety profile of Exemestane Taj Pharma, no dose adjustment is considered to be necessary.

Hepatic impairment.

In patients with moderate or severe hepatic impairment the exposure of Exemestane Taj Pharma is 2-3 fold higher compared with healthy volunteers. Given the safety profile of Exemestane Taj Pharma, no dose adjustment is considered to be necessary.

5.3 Preclinical safety data

Toxicological studies: Findings in the repeat dose toxicology studies in rat and dog were generally attributable to the pharmacological activity of Exemestane Taj Pharma, such as effects on reproductive and accessory organs. Other toxicological effects (on liver, kidney or central nervous system) were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Mutagenicity: Exemestane Taj Pharma was not genotoxic in bacteria (Ames test), in V79 Chinese hamster cells, in rat hepatocytes or in the mouse micronucleus assay. Although Exemestane Taj Pharma was clastogenic in lymphocytes *in vitro*, it was not clastogenic in two *in vivo* studies.

Reproductive toxicology*:* Exemestane Taj Pharma was embryotoxic in rats and rabbits at systemic exposure levels similar to those obtained in humans at 25mg/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 450mg/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 (450mg/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 Taj Pharma.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol, Cellulose Microcrystalline, Crospovidone, Sodium starch Glycolate , Hypromellose, Polysorbate 80, Colloidal Anhydrous Silica, Magnesium stearate, Hypromellose , Macrogol, Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Exemestane Taj Pharma 25mg Tablets are packed in White opaque PVC/PVdC-Alu blister.

Pack size:

15, 20, 28 30, 60, 90, 98, 100 and 120 tablets in blister packs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured in India By:
TAJ PHARMACEUTICALS LIMITED
at SURVEY NO.188/1 TO 189/1,190/1 TO 4, ATHIYAWAD, DABHEL, DAMAN-396210 (INDIA)