PACKAGE INSERT
(For the use of a Registered Medical Practitioner or a Hospital)

1. NAME OF THE MEDICINAL PRODUCT

EXACCORD 25 (Exemestane Tablets 25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Exemestane 25 mg

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, biconvex film coated tablets debossed with 'E25' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Exemestane 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 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 is one 25 mg tablet to be taken once a 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 tumour relapse occurs.

In patients with advanced breast cancer, treatment with Exemestane 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 Contra-indications

Exemestane tablets are contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and 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.

Exemestane 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, women with osteoporosis or at risk of osteoporosis should have 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 are not available, patients treated with Exemestane 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 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, a potent CYP450 inducer, at a dose of 600mg daily and a single dose of exemestane 25mg, 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 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 coadministered with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Exemestane should not be used 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).

Breast-feeding
It is not known whether exemestane is excreted into human milk. Exemestane 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 was generally well tolerated across all clinical studies conducted with Exemestane at a standard dose of 25 mg/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 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 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).

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
Uncommon	asthenia

(*) Includes: arthralgia, and less frequently pain in extremity, osteoarthritis, back pain, arthritis, myalgia and joint stiffness
(†) 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 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 = 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 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, gastric ulcer was observed at a higher frequency in the exemestane arm compared to tamoxifen (0.7% versus <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 postmenopausal 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
ATC: L02BG06
Mechanism of action
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 postmenopausal women. In postmenopausal women, Exemestane p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

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.

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 (25 mg/day) or tamoxifen (20 or 30 mg/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 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 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 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 (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. 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).

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

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 = 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 following 2 to 3 years of tamoxifen treatment experienced moderate reduction in bone mineral density.

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-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.

IES 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. Results showed that in the observed study period Exemestane 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 over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy or hormonal therapy.

In addition, 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 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 (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. 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 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 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 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 and -3.44 [spine], -4.15 [total hip] for tamoxifen).

IES 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 oestrogen 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% versus. 12.4%).

Treatment of Advanced Breast Cancer

In a randomised peer reviewed controlled clinical trial, Exemestane 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 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 tablets, exemestane 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. Concomitant intake with food increases the bioavailability by 40%.

Distribution

The volume of distribution of exemestane, 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 and its metabolites do not bind to red blood cells.

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

Elimination

Exemestane is metabolised by oxidation of the methylene moiety on the 6 position by CYP3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane 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 were eliminated within a week.

Special populations

Age

No significant correlation between the systemic exposure of Exemestane 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 was 2 times higher compared with healthy volunteers.

Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

Hepatic impairment

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

Toxicological studies: Findings in the repeat dose toxicology studies in rat and dog were generally attributable to the pharmacological activity of exemestane, 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 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:
Mannitol
Microcrystalline Cellulose
Crospovidone
Sodium starch Glycolate
Hypromellose E5
Polysorbate 80
Colloidal Anhydrous Silica
Magnesium stearate

Tablet Coating
Hypromellose 6cp (E464)
Macrogol (400)
Titanium dioxide (E171)

6.2 Shelf life

Refer to Expiry Date on outer carton.

6.3 Special precautions for storage

Do not store above 30 °C.

6.4 Nature and contents of container

Exemestane Tablets 25 mg is available in White opaque PVC/PVDC - Alu blister pack of 10 Tablets. Each carton contains 3 such blisters. (3 X 10 Tablets)

7. NAME AND ADDRESS OF PRODUCT LICENCE HOLDER

Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

8. DATE OF REVISION OF PACKAGE INSERT

August 2020