Package Insert

1. Name of the medicinal product

Exedral 25, 25 mg film-coated tablets

2. Name and Strength of the Active Substance

Each film coated tablet contains 25 mg exemestane.

3. Description of the Product

Film-coated tablet.

White, round biconvex film-coated tablets.

List of excipients:
Tablet Core:
Silica, colloidal anhydrous
Crospovidone
Hypromellose 5cP
Magnesium stearate
Mannitol
Microcrystalline cellulose
Polysorbate 80
Sodium starch glycolate (Type A)

Film-coating:
Hypromellose 5cP
Macrogol
Talc
Titanium dioxide (E171)

4. Pharmacodynamics / Pharmacokinetics

Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme therapy; Hormone antagonists and related agents, ATC code: 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 (Intergroup Exemestane Study [IES]), conducted in 4,724 post-menopausal 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 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 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 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), 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 oestrogen receptor-positive patients are summarised 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 = 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 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 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.

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 the 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 favour 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 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% vs. 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 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.

Pharmacokinetic properties

Absorption
After oral administration 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 17 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 impairement
In patients with severe renal impairment ($CL_{cr} \leq 30$ 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 impairement
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.

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.

Reproductive toxicology

In animal reproduction studies in rats and rabbits, exemestane was embryotoxic, fetotoxic, and abortifacient. Radioactivity related to 14C-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/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).

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.

5. 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.

6. Recommended Dosage

Posology

Adults and elderly patients

The recommended dose of exemestane is one 25 mg tablet to be taken orally 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 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 section 4).

Peadiatric population
Not recommended for use in children.

7. Mode/Route of Administration

Oral administration.

8. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 3. In pre-menopausal women and in pregnant or breastfeeding women.

9. Warnings and Precautions

Exemestane should not be administered to women with pre-menopausal endocrine status. Therefore, whenever clinically appropriate, the post-menopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

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

As exemestane is a potent estrogen lowering agent, reductions in bone mineral density can be anticipated. 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 osteopososis 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 in women with early breast cancer. Women with Vitamin D deficiency should receive supplementation with Vitamin D.

This product contains sodium.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

10. 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 4) 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.

In an interaction study with rifampicin, a potent CYP450 inducer, at a dose of 600 mg 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 medicinal products, 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 medicinal products 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 medicines.

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

11. Use during Pregnancy / Lactation

Pregnancy
No clinical data on exposed pregnancies are available with exemestane. Studies on animals have shown reproductive toxicity (see section 4). Exemestane is therefore contraindicated in pregnant women.

Breastfeeding
It is not known whether exemestane is excreted into human milk. Exemestane should not be administered to women that are breastfeeding.

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 8 and 9).

Effects on ability to drive and use machines

Exemestane has moderate influence on the ability to drive and use machines.

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of exemestane. 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.

12. Adverse Effects / Undesirable Effects

Clinical Trials:

Exemestane was generally well tolerated across all studies and in the clinical studies, conducted with exemestane 25 mg/day, adverse effects 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 oestrogen deprivation (eg hot flushes).

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 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); Very rare (< 1/10,000); 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, paresthesia*
Uncommon	Somnolence
Vascular disorders:	
Very common	Hot flushes
Gastrointestinal disorders:	

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

Hepatobiliary disorders	
Rare	Hepatitis*§, hepatitis cholestatic*§
Skin and subcutaneous tissue disorders:	
Very common	Hyperhidrosis
Common	Alopecia, rash, urticaria*, pruritus*
Rare	Acute generalizes exanthematous pustulosis*§
Musculoskeletal and bone disorders:	
Very common	Joint and musculoskeletal pain[a]
Common	Fracture, osteoporosis
Uncommon	Trigger finger*
Rare	Tenosynvitis stenosans*§
General disorders and administration site conditions:	
Very common	Pain, fatigue
Common	Edema peripheral
Uncommon	Asthenia
Investigations	
Very common	Hepatic enzyme increased, blood bilirubin increased, blood alkaline phosphatase increased

* Adverse drug reaction identified post-marketing

§ Adverse drug reaction frequency represented by the estimated upper limit of the 95% confidence interval calculated using the 'Rule of 3'.

[a] Includes: arthralgia, and less frequently pain in limb, osteoarthritis, back pain, arthritis, myalgia and joint stiffness.

In patients with advanced breast cancer, 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%)
Hyperhidrosis	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%)
Gynaecological	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%)

13. Overdose and Treatment

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.

14. Incompatibilities

Not applicable.

15. Storage Condition

Do not store above 30 °C. Protect from light and moisture.

16. Shelf Life

2 years.

17. Presentation

PVC/PE/PVDC – aluminium blisters. Pack size of 30 film-coated tablets.

18. Name and Address of Manufacturer

Remedica Ltd,
Aharnon Street, Limassol Industrial Estate,
3056 Limassol, Cyprus

19. Date of revision of the text

For internal use only: sg-pi-exedral-fc-tabs-a4