

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Exemestane Pfizer® 25 mg coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: exemestane.

Each coated tablet contains 25 mg exemestane.

Excipient(s) with known effect

Each tablet contains 30.2 mg of sucrose and 0.003 mg of methyl parahydroxybenzoate (E218).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar-coated tablets for oral administration.

The tablets are imprinted “7663” on one side with black printing ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXEMESTANE PFIZER is indicated for:

- the adjuvant treatment of postmenopausal women with oestrogen receptor positive or receptor unknown early breast cancer after initial adjuvant tamoxifen to reduce the risk of recurrence (distant and loco-regional) and contralateral breast cancer
- the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy
- the third-line hormonal treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease progressed following treatment with anti-oestrogens and either non-steroidal aromatase inhibitors or progestins.

4.2 Dose and method of administration

Dose

Adult and elderly patients

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

In patients with early breast cancer, treatment should continue until completion of five years adjuvant hormonal therapy, or until tumour relapse occurs.

In patients with advanced breast cancer, treatment with EXEMESTANE PFIZER should continue until tumour progression is evident.

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

Paediatric population

Not recommended for use in children.

4.3 Contraindications

EXEMESTANE PFIZER tablets are contraindicated in:

- Pregnant or lactating women.
- Patients with Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As EXEMESTANE PFIZER is a potential oestrogen lowering agent, reduction in bone mineral density can be anticipated. During adjuvant treatment with EXEMESTANE PFIZER, women with osteoporosis or at risk of developing osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Patients treated with EXEMESTANE PFIZER should be carefully monitored. Treatment or prophylaxis for osteoporosis should be initiated as appropriate.

Because of its mode of action, EXEMESTANE PFIZER should not be administered to women with pre-menopausal endocrine status. Whenever clinically appropriate, confirmation of post-menopausal status may be assisted by laboratory tests, such as assessment of luteinising hormone (LH), follicle stimulating hormone (FSH) and oestradiol levels.

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.

Effects on laboratory tests

Elevation of serum hepatic function test (especially ALT and GGT) and alkaline phosphatase have been occasionally observed. In the pivotal controlled study these elevations occurred mainly in patients with liver or bone metastasis or other impaired liver conditions, except for the elevations in GGT. Decreases in WBC, especially lymphocytes, were also observed.

4.5 Interaction with other medicines and other forms of interaction

EXEMESTANE PFIZER should not be coadministered with oestrogen-containing products as these would negate its pharmacological action.

No formal drug interaction studies have been carried out. *In vitro* evidence showed that the drug is metabolised 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 CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of exemestane.

A possible decrease of exemestane plasma levels by known inducers of CYP 3A4 cannot be excluded.

EXEMESTANE PFIZER should be used cautiously with drugs that are metabolised via CYP 3A4 and have a narrow therapeutic window.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C.

Exemestane should not be used in women who are or may become pregnant because it may cause harm to the fetus (see section 4.3). Exemestane disrupts oestrogen dependent metabolism and may result in abortion. Studies in animals have shown reproductive toxicity (see section 5.3).

There are no studies in pregnant women using EXEMESTANE PFIZER. EXEMESTANE PFIZER is contraindicated in pregnant women and only indicated for postmenopausal women. If there is exposure to EXEMESTANE PFIZER during pregnancy, the patient should be advised of the potential hazard to the fetus and potential risk for loss of the pregnancy.

Breast-feeding

Exemestane and/or its metabolites appeared in rat milk within 15 minutes of oral administration of radiolabelled exemestane. Concentrations of exemestane and its metabolites were approximately equivalent in the milk and plasma of rats for 24 hours after a single oral dose of 1 mg/kg ¹⁴C-exemestane. It is not known whether exemestane is excreted in human milk. Because many drugs are excreted in human

milk, EXEMESTANE PFIZER should not be used in women who are lactating (see section 4.3).

Fertility

Untreated female rats showed reduced fertility when mated to males treated with 500 mg/kg/day exemestane (approximately 200 times the recommended human dose on a mg/m² basis). Exemestane given to female rats showed no effects on female fertility parameters (e.g. ovarian function, mating behaviour, conception rate) at doses up to 20 mg/kg/day (approximately 8 times the human dose on a mg/m² basis), but mean litter size was decreased at this dose. In general toxicology studies, changes in the ovary, including hyperplasia, an increase in ovarian cysts and a decrease in corpora lutea were observed with variable frequency in mice, rats and dogs at doses that ranged from 3-20 times the human dose on a mg/m² basis.

4.7 Effects on ability to drive and use machines

EXEMESTANE PFIZER is unlikely to impair the ability of patients to drive and operate machinery. However, 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

In clinical studies conducted with EXEMESTANE PFIZER 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 PFIZER 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%).

Treatment emergent adverse events and illnesses including all causalities and occurring with an incidence of $\geq 5\%$ in either treatment group in study 031 during or within one month of the end of the study are shown in Table 1.

Table 1. Incidence (%) of Adverse Events of all Grades¹ and Illnesses Occurring in \geq 5% of Patients in Any Treatment Group in Study 031 in Postmenopausal Women with Early Breast Cancer

	% of patients	
Body system and adverse events by MedDRA dictionary	EXEMESTANE PFIZER 25 mg daily (N=2252)	Tamoxifen 20 mg daily ² (N=2280)
<u>Cardiac disorders</u> Cardiovascular disorders ³	12.8	10.6
<u>Eye</u> Visual disturbances ³	5.0	3.8
<u>Gastrointestinal</u> Nausea ³	8.5	8.7
<u>General disorders</u> Fatigue ³	16.1	14.7
<u>Investigations</u> Weight increased	5.5	5.8
<u>Musculoskeletal</u> Arthralgia Pain in limb Back pain Osteoarthritis	14.6 9.0 8.6 5.9	8.6 6.4 7.2 4.5
<u>Nervous</u> Headache ³ Dizziness ³ Carpal tunnel syndrome	13.1 9.7 2.4	10.8 8.4 0.2
<u>Psychiatric</u> Insomnia ³ Depression	12.4 6.2	8.9 5.6
<u>Skin & Subcutaneous Tissue</u> Increased sweating ³	11.8	10.4
<u>Vascular</u> Hot flushes ³	21.2	19.9

1 - Graded according to Common Toxicity Criteria;

2 - 75 patients received tamoxifen 30 mg daily;

3 - Event actively sought.

In patients with advanced breast cancer, the adverse events in which a causal relationship with EXEMESTANE PFIZER could not be excluded are listed below by system organ class and by frequency. Frequencies are defined as: very common (\geq 10%), common (\geq 1%, <10%), uncommon (\geq 0.1%, <1%), rare (\geq 0.01%, <0.1%).

General disorders and administration site conditions

Very common: Pain, fatigue.

Common: Peripheral oedema (including leg oedema).

Gastrointestinal disorders

Very common: Abdominal pain, nausea.

Common: Vomiting, diarrhoea, constipation, dyspepsia.

Hepatobiliary disorders

Very common: Hepatic enzyme increased (including ALT increased), blood bilirubin increased, blood alkaline phosphatase increased.

Metabolism and nutrition disorders

Common: Anorexia.

Nervous system disorders

Very common: Headache, dizziness.

Common: Carpal tunnel syndrome.

Psychiatric disorders

Very common: Depression, insomnia.

Vascular disorders

Very common: Hot flushes.

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.

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

In the early breast cancer trial, the frequency of ischaemic cardiac events in the EXEMESTANE PFIZER 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 early breast cancer trial, gastric ulcer was observed at a slightly 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.

Elevation of liver function test parameters including enzymes, bilirubin and alkaline phosphatase have been observed.

Treatment emergent adverse events considered drug-related or of indeterminate cause, and which occurred in $\geq 2\%$ of patients in a phase III clinical trial comparing exemestane and megestrol acetate, are summarised in Table 2.

Table 2. Drug-related or of indeterminate cause adverse events of any grade in $\geq 2\%$ of patients from a phase III study

Body system/Adverse event	% EXEMESTANE PFIZER 25 mg once daily (N=358)	% Megestrol acetate 40 mg qid (N=400)
<i>Any adverse event</i>	39.1	45.8
<i>Autonomic nervous system</i>	4.7	7.5
Increased sweating	4.5	7.5
<i>Body as a whole</i>	20.7	21.0
Fatigue	7.5	10.3
Hot flushes	12.6	5.0
Oedema legs	1.4	2.8
Pain	2.8	2.8
<i>Cardiovascular</i>	2.0	4.5
Hypertension	1.7	3.3
<i>Central and peripheral nervous system</i>	7.0	8.8
Dizziness	3.4	3.0
Headache	2.5	1.5
<i>Gastrointestinal</i>	18.2	21.5
Abdominal pain	2.8	4.3
Nausea	9.2	5.0
Appetite increased	2.8	5.8
Constipation	0.8	2.5
Vomiting	2.8	0.8
<i>Psychiatric</i>	7.3	6.5
Insomnia	3.6	3.3
<i>Reproductive event, female</i>	2.0	3.5
Vaginal haemorrhage	0.6	2.5
<i>Respiratory</i>	2.2	5.5
Dyspnoea	0.3	3.0
<i>Skin and appendages</i>	7.0	3.0
Rash	2.0	0

An occasional decrease in lymphocytes has been observed in approximately 20% of patients receiving EXEMESTANE PFIZER, 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. Thrombocytopenia and leukopenia have been occasionally reported.

Elevation of serum hepatic function tests (especially ALT and GGT) and alkaline phosphatase have been occasionally observed. In the pivotal controlled study, these

elevations occurred mainly in patients with liver or bone metastasis or other impaired liver conditions except for the elevations in GGT.

Post-marketing experience

Immune system disorders

Hypersensitivity.

Nervous system disorders

Paraesthesia.

Hepatobiliary disorders

Rare cases of hepatitis including cholestatic hepatitis have been observed in clinical trials and reported through post-marketing surveillance.

Skin and subcutaneous tissue disorders

Urticaria, pruritus, acute generalised exanthematous pustulosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Clinical trials have been conducted with EXEMESTANE PFIZER 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 PFIZER 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/m² basis.

There is no specific antidote to overdosage and treatment should be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Haemodialysis is not expected to significantly enhance the clearance of EXEMESTANE PFIZER due to extensive protein binding.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics effects

Pharmacotherapeutic group: steroidal aromatase inhibitor; anti-neoplastic agent

ATC code: L02BG06

Mechanism of action

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In postmenopausal 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. Exemestane acts by binding irreversibly to the active site of the enzyme causing its inactivation. Such type of inactivation is also known as “suicidal inhibition”. In postmenopausal women, EXEMESTANE PFIZER significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (80-90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatisation 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 trials with multiple daily doses, 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 expected for the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in oestrogen levels stimulating the pituitary secretion of gonadotropins. A dose-related decrease in SHBG was observed, which occurred with exemestane 25 mg/day.

Clinical efficacy and safety

Adjuvant treatment of early breast cancer

In a multicentre, randomised, double-blind study (number 031), 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 PFIZER (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)

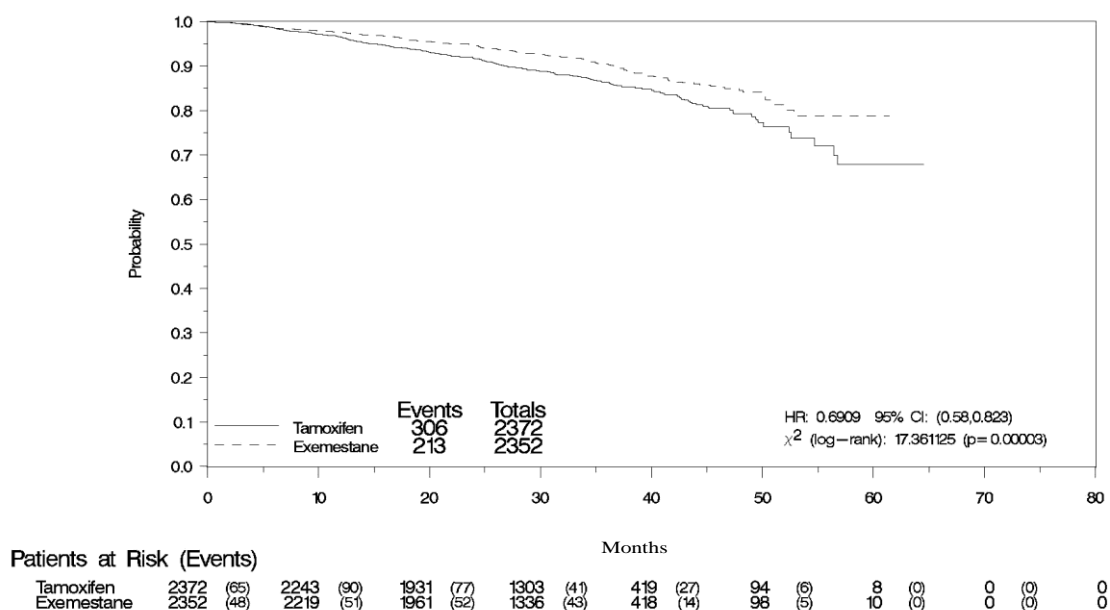
After a median duration of therapy of about 27 months and a median follow-up of about 35 months, results showed that sequential treatment with EXEMESTANE PFIZER after 2 to 3 years of adjuvant tamoxifen therapy was associated with a clinically and statistically significant improvement in disease-free survival (DFS), compared with continuation of tamoxifen therapy. Analysis showed that in the observed study period EXEMESTANE PFIZER reduced the risk of breast cancer recurrence by 31% compared to 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 PFIZER 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 PFIZER group and 137 in the tamoxifen group (hazard ratio 0.86; p=0.23).

Table 3. Efficacy Results from Study 031 in Postmenopausal Women with Early Breast Cancer

	Hazard Ratio	
	Hazard Ratio (95% CI)	p-value (log-rank test)
Disease free survival	0.69 (0.58-0.82)	0.00003
Breast cancer free survival*	0.65 (0.54-0.79)	<0.00001
Time to contralateral breast cancer	0.32 (0.15-0.72)	0.00340
Distant recurrence free survival	0.70 (0.58-0.86)	0.00083
Overall survival	0.86 (0.67-1.10)	0.22962

* In this analysis deaths of patients who did not have a recurrence or contralateral breast cancer were censored

Figure 1. Disease Free Survival in Study 031 of Postmenopausal Women with Early Breast Cancer



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 PFIZER 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 PFIZER reduced the risk of breast cancer recurrence by 24% compared with tamoxifen (hazard ratio 0.76, p = 0.00015). The beneficial effect of EXEMESTANE PFIZER over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

EXEMESTANE PFIZER also significantly reduced risk of contralateral breast cancer (hazard ratio 0.57, p = 0.04158), significantly prolonged breast cancer-free survival (hazard ratio 0.76, p = 0.00041), and distant recurrence-free survival (hazard ratio 0.83, p = 0.02621).

In the whole study population, a trend for improved overall survival was observed for EXEMESTANE PFIZER (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 favour of EXEMESTANE PFIZER. 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 a bone substudy demonstrated that women treated with EXEMESTANE PFIZER following 2 to 3 years of tamoxifen treatment moderately increased bone loss. However the fracture incidence was not statistically different in patients treated with EXEMESTANE PFIZER and tamoxifen (3.1% and 2.3% respectively).

Results from an endometrial substudy indicate that after 2 years of treatment there was a 33% reduction of endometrial thickness in the EXEMESTANE PFIZER 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 PFIZER.

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

EXEMESTANE PFIZER 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 PFIZER 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 PFIZER 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 PFIZER 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 PFIZER 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%).

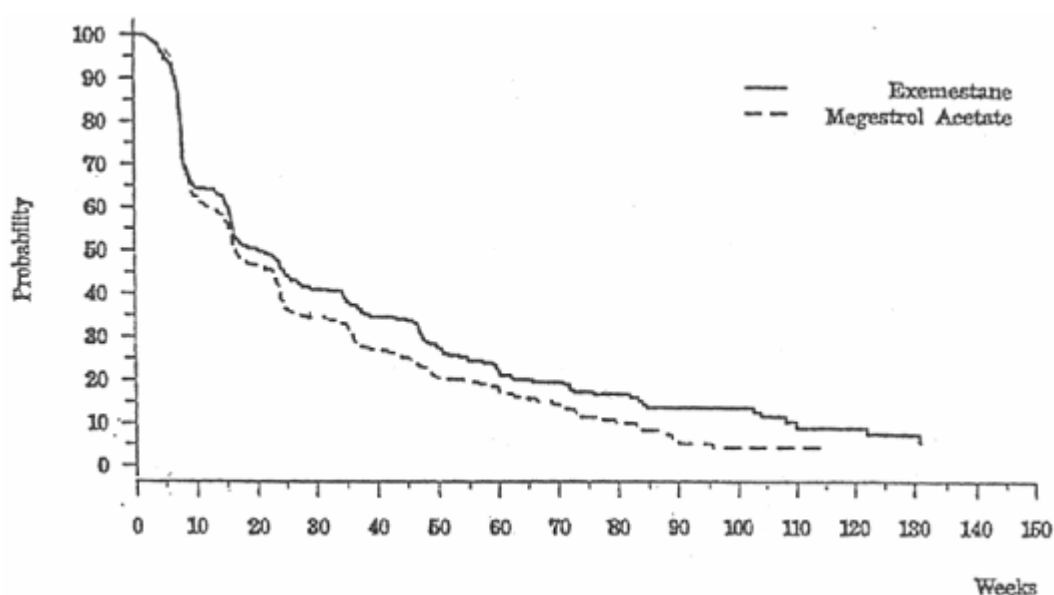
Treatment of advanced breast cancer

Efficacy data in patients progressing while on anti-oestrogen therapy (second-line treatment) include results from a phase III study (multicentre, multinational, peer-reviewed, randomised, double-blind, controlled) with EXEMESTANE PFIZER 25 mg daily versus megestrol acetate 40 mg 4 times a day (qid) in 763 patients. All patients had failed on prior tamoxifen treatment. The population characteristics were representative of postmenopausal patients with relapsed advanced breast cancer. The median age was 65 years. Various races were represented, the majority being Caucasian. Most patients (70%) were oestrogen receptor/progesterone receptor positive and most had measurable disease. Almost 50% had predominantly visceral disease.

The peer-reviewed results of this controlled study indicate that EXEMESTANE PFIZER and megestrol acetate are equivalent in terms of objective responses, with objective response rates of 12.4% for megestrol acetate versus 15.0% for EXEMESTANE PFIZER (C.I. for difference -7.5+2.3). Overall success rates (Complete Response, Partial Response or No Change) are also comparable, 37.4% for EXEMESTANE PFIZER versus 34.6% for megestrol acetate.

Conversely, duration of overall success (median: 60.1 versus 49.1 weeks, $p=0.025$), time to progression (median: 20.3 versus 16.6 weeks, $p=0.037$), time to treatment failure (median: 16.3 versus 15.7 weeks, $p=0.042$), and survival (median not yet achieved versus 123.4 weeks, $p=0.039$) are significantly longer in EXEMESTANE PFIZER -treated patients than in those treated with megestrol acetate. The point estimates for survival at the 25th percentile (75% survival) are 74.6 weeks (95% C.I. 59.1 - 91.0) for EXEMESTANE PFIZER and 55.0 weeks (95% C.I. 46.1 - 70.3) for megestrol acetate. The Kaplan-Meier curve for time to tumour progression is shown in Figure 2.

Figure 2. Time to tumour progression in the comparative study of EXEMESTANE PFIZER and megestrol acetate



Efficacy was also observed in patients having progressed following multiple hormone therapies (third-line therapy). Three peer-reviewed uncontrolled phase II studies were conducted at the recommended dose of 25 mg EXEMESTANE PFIZER. In the combined analysis, which was of the descriptive type, EXEMESTANE PFIZER induced objective response, with a median duration of 61 weeks, in 9% of the patients (95% C.I. 6-12) and overall clinical benefit, with a median duration of 37 weeks, in 26% of the cases (95% C.I. 22-31). Although survival cannot yet be estimated in each of the three studies, median survival in the overall population (intent-to-treat) was approximately 30 months (131.1 weeks, 95% C.I. 100.0 - 147.1 weeks). EXEMESTANE PFIZER was effective both in patients experiencing failure of megestrol acetate and failure of other non-steroidal aromatase inhibitors.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, exemestane is rapidly and extensively absorbed, although animal data suggest that the absolute bioavailability was low due to an extensive first-pass effect. At a single dose of 25 mg given after a meal, average peak plasma levels of 18 ng/mL are achieved within 2 hours post-dosing. Food was shown to enhance absorption, resulting in plasma levels 30-40% higher than those observed in subjects under fasting conditions.

Distribution

After the peak, plasma levels of exemestane decline in a polyexponential manner with a terminal half-life of approximately 24 hours. The plasma protein binding of exemestane is approximately 90% and the fraction bound is independent of total concentration. The distribution of the drug and/or its metabolites into blood cells is negligible.

Biotransformation and elimination

No significant deviations from dose-proportional pharmacokinetics were observed in healthy volunteers up to a 50 mg oral dose. Following repeated daily administration of 25 mg, plasma concentrations of the unchanged drug were of a similar order to those measured after single dosing. Following oral administration of a single dose of radiolabelled exemestane, the elimination of drug-related products was shown to be essentially complete within 1 week, with approximately equal proportions of the dose eliminated in urine and faeces. The amount of drug excreted unchanged in urine is less than 1% of the dose. The biotransformation proceeds through oxidation of the methylene group at position 6 via the CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductases. Subsequently, many secondary metabolites are formed, each accounting for a limited amount of the dose. The metabolites are either inactive or less active than the parent drug in inhibiting aromatase.

Special populations

Age

No significant correlation between the systemic exposure of exemestane and the age of subjects has been observed.

Renal impairment

Exemestane pharmacokinetics have been investigated in subjects with severe renal insufficiency ($CL_{CR} \leq 30$ mL/min). In these subjects the systemic exposure to exemestane after a single dose was found to be approximately double that of healthy volunteers. This difference, although pharmacokinetically significant, is unlikely to require dose adjustment, given the good tolerability observed in humans at doses up to 8 times the recommended dose. However, EXEMESTANE PFIZER should be used with caution in patients with renal insufficiency.

Hepatic impairment

Exemestane pharmacokinetics have been investigated in subjects with moderate and severe hepatic insufficiency. The systemic exposure to exemestane was 2-3 times higher than in healthy volunteers. As for renal insufficiency, dose adjustment is unlikely to be required. However, EXEMESTANE PFIZER should be used with caution in patients with hepatic insufficiency.

5.3 Preclinical safety data

Mutagenicity

Exemestane was not mutagenic in bacteria (Ames test), in V79 Chinese hamster cells nor did it cause DNA damage in rat hepatocytes. Although exemestane was clastogenic in lymphocytes *in vitro*, it was not clastogenic in two *in vivo* studies.

Carcinogenicity

A two-year carcinogenicity study in mice at doses of 50, 150 and 450 mg/kg/day exemestane (gavage) resulted in an increased incidence of hepatocellular adenomas and/or carcinomas in both genders at the high dose level. Plasma $AUC_{(0-24hr)}$ at the high dose were 2575 ± 386 and 5667 ± 1833 ng.hr/mL in males and females (approx. 34 and 75 fold the AUC in postmenopausal patients at the recommended clinical dose). An increased incidence of renal tubular adenomas was observed in male mice at the high dose of 450 mg/kg/day. Since the doses tested in mice did not achieve an MTD, neoplastic findings in organs other than liver and kidneys remain unknown.

A separate carcinogenicity study was conducted in rats at doses of 30, 100 and 315 mg/kg/day (gavage) for 92 weeks in males and 2 years in females. No evidence of carcinogenic activity up to the highest dose tested (315 mg/kg/day) was observed in females. The male rat study was inconclusive since it was terminated prematurely at week 92. At the highest dose, plasma $AUC_{(0-24hr)}$ levels in male (1418 ± 287 ng.hr/mL) and female (2318 ± 1067 ng.hr/mL) rats were 19 and 31 fold higher than

those measured in the postmenopausal cancer patients, receiving the recommended clinical dose.

Reproductive toxicity

In animal reproduction studies in rats and rabbits, exemestane was embryotoxic, fetotoxic, and abortifacient. In rats the concentration of exemestane and its metabolites was approximately equivalent in maternal and foetal 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). Prolonged gestation and abnormal or difficult labour were 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). Increased resorption, reduced number of live foetuses, decreased foetal weight and retarded ossification were also observed at these doses. No malformations were noted when exemestane was administered to pregnant rats during the organogenesis period at doses up to 810 mg/kg/day (approximately 320 times the recommended human 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). In the presence of maternal toxicity, abortions, an increase in resorptions and a reduction in foetal body weight were seen at 270 mg/kg/day (approximately 210 times the recommended human dose on a mg/m² basis). There was no increase in the incidence of malformations in rabbits at doses up to 270 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal hydrated silica

Crospovidone

Hypromellose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Sodium starch glycollate

Polysorbate 80

Tablet coating

Hypromellose

Polyvinyl alcohol

Simethicone

Macrogol 6000

Sucrose

Magnesium carbonate, light

Titanium dioxide (E171)

Methyl parahydroxybenzoate (E218)

Cetyl esters wax

Purified talc

Carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

25 mg tablets in blister packs: 30's.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Ltd
PO Box 3998
Auckland, New Zealand
Toll Free number: 0800 736 363

9. DATE OF FIRST APPROVAL

30 May 2002.

10. DATE OF REVISION OF THE TEXT

30 April 2018

Summary of updates (30 April 2018)

Section	Update
Section 5.1	Addition of long-term 87 months and 119 months follow-up clinical data