AUSTRALIAN PRODUCT INFORMATION - AROMASIN® (EXEMESTANE) TABLETS

1. NAME OF THE MEDICINE

Exemestane

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mg tablet contains 25 mg exemestane

Excipients with known effect

Each tablet contains 30.2 mg of sucrose and 0.003 mg of methyl hydroxybenzoate.

For the full list of excipients, see Section 6.1, List of Excipients.

3. PHARMACEUTICAL FORM

AROMASIN tablets are 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

AROMASIN is indicated for the sequential adjuvant treatment of estrogen receptor-positive early breast cancer in postmenopausal women who have received prior adjuvant tamoxifen therapy.

AROMASIN is indicated for the treatment of estrogen receptor-positive advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-estrogen therapy.

4.2 Dose and method of administration

Adults

The recommended dose of AROMASIN in adults is one 25 mg tablet 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 AROMASIN should continue until tumour progression is evident.

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

Paediatric use

Not recommended for use in children.

4.3 Contraindications

AROMASIN tablets are contraindicated in pregnant or lactating women and in patients with a known hypersensitivity to the medicine or to any of the excipients.

4.4 Special warnings and precautions for use

Check the following before use.

Because of its mode of action, AROMASIN should not be administered to women with premenopausal endocrine status. Whenever clinically appropriate, confirmation of postmenopausal status may be assisted by laboratory tests, such as assessment of luteinising hormone (LH), follicle stimulating hormone (FSH) and estradiol 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. Women with Vitamin D deficiency should receive supplementation with Vitamin D.

Bone mineral density and fracture risk

Overall, in trial 031, the incidence of fracture was greater in patients treated with AROMASIN than tamoxifen (see Section 4.8, Adverse effects (undesirable effects)). Treatment-emergent fractures were more frequent in AROMASIN patients (4.5%) than in tamoxifen patients (3.3%). When all fractures reported on-treatment and during follow-up are considered, the incidence was significantly greater in AROMASIN patients (7.3%) compared with tamoxifen patients (5.2%), p=0.004.

Reductions in bone mineral density (BMD) over time are seen with AROMASIN use. In a sub-study of trial 031 in early breast cancer, patients who received 2-3 years of AROMASIN after 2-3 years of tamoxifen (n=86) had a higher loss of BMD while on treatment than patients who received continuous tamoxifen (n=100) (mean % change from baseline for BMD at 36 months: -3.37 [spine], -2.96 [total hip] for AROMASIN and -1.29 [spine], -2.02 [total hip], for tamoxifen).

As AROMASIN is a potent estrogen lowering agent, reduction in BMD can be anticipated. During adjuvant treatment with AROMASIN, women with osteoporosis or at risk of developing osteoporosis should have their BMD formally assessed by bone densitometry at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

Tendon disorders

The use of third generation aromatase inhibitors, including exemestane, were found to be associated with tendonitis and tenosynovitis in randomised controlled trials. Tendon rupture

was found to be a potential risk associated with third generation aromatase inhibitors. Monitor patients for signs and symptoms of tendon disorders during treatment with AROMASIN.

Use in hepatic impairment

See Section 5.2, Pharmacokinetic properties.

Use in renal impairment

See Section 5.2, Pharmacokinetic properties.

Use in the elderly

No data available.

Paediatric use

Not recommended for use in children.

Effects on laboratory tests

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. Decreases in WBC, especially lymphocytes, were also observed.

4.5 Interactions with other medicines and other forms of interactions

AROMASIN should not be coadministered with estrogen-containing products as these would negate its pharmacological action.

No formal drug interaction studies have been carried out. *In vitro* evidence showed that the medicine 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. AROMASIN should be used cautiously with drugs that are metabolised via CYP 3A4 and have a narrow therapeutic window.

4.6 Fertility, pregnancy and lactation

Effects on 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/m^2 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/m^2 basis), but mean litter size was decreased at this dose. In general toxicology studies, changes in the ovary, including atrophy, tubulo-stromal hyperplasia, an increase in ovarian cysts and a decrease in corpora lutea were observed with variable frequency in mice, rats and/or dogs at doses that ranged from 3-20 times the human dose on a mg/m^2 basis.

Use in 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, Contraindications). Exemestane disrupts estrogen dependent metabolism and may result in abortion. Studies in animals have shown 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 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). 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/m^2 basis). Increased resorption, reduced number of live fetuses, decreased fetal 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/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). 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). There was no increase in the incidence of malformations in rabbits at doses up to 270 mg/kg/day.

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

Use in lactation

AROMASIN is contraindicated in pregnant women and only indicated in postmenopausal women. 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 ^{14}C-exemestane. It is not known whether exemestane is excreted in human milk. Because many drugs are excreted in human milk, AROMASIN should not be used in women who are lactating.

4.7 Effects on ability to drive and use machines

AROMASIN 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 medicine. 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 Adverse effects (undesirable effects)

AROMASIN was generally well tolerated across all clinical studies; 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 AROMASIN following initial adjuvant tamoxifen therapy. The most commonly reported adverse reactions were hot flush (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 flush (14%) and nausea (12%).

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

Adverse events in which a causal relationship with AROMASIN could not be excluded are listed below by system organ class and by frequency. Frequencies are defined as: very common (≥10%), common (≥1%, <10%), uncommon (≥0.1%, <1%), rare (≥0.01%, <0.1%).

General disorders and administration site conditions

Very common: Pain, fatigue.

Common: Peripheral oedema (including leg oedema), asthenia.

Gastrointestinal disorders

Very common: Abdominal pain, nausea.

Common: Vomiting, diarrhoea, constipation, dyspepsia.

Investigations

Very common: Hepatic enzyme increased (including ALT increased, GGT 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.

Rare: Somnolence

Psychiatric disorders

Very common: Depression, insomnia.

Vascular disorders

Very common: Hot flush.

Skin and subcutaneous tissue disorders

Very common: Hyperhidrosis.

Common: Alopecia, rash.

Musculoskeletal and connective tissue disorders

Very common: Joint and musculoskeletal pain[∞].

Common: Fracture, osteoporosis.

Blood and lymphatic system disorders

Very common: Leukopenia[#]

Uncommon: Thrombocytopenia[#]

Unknown: Lymphocyte decrease[#]

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

[#] Events observed in patients with advanced breast cancer.

Treatment emergent adverse events and illnesses including all causalities and occurring with an incidence of ≥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. Adverse events[1] and illnesses with incidence ≥5% and/or a significant difference[‡] between AROMASIN and tamoxifen in study 031 in early breast cancer (median follow-up about 52 months)

Body system and adverse events by MedDRA dictionary	% of patients	
	AROMASIN 25 mg daily (N=2249)	**Tamoxifen 20 mg daily[2] (N=2279)**
Cardiovascular		
Hypertension	9.9	8.4
Thromboembolism[‡]	0.7	1.8
Gastrointestinal		
Nausea[3]	8.9	9.1
Diarrhoea[‡]	4.2	2.2
Gastric ulcer[‡]	0.7	<0.1
General disorders		
Hot flush	21.8	20.1
Fatigue[3]	16.3	15.1

Body system and adverse events by MedDRA dictionary	% of patients	
	AROMASIN 25 mg daily (N=2249)	**Tamoxifen 20 mg daily[2] (N=2279)**
Gynaecological		
Vaginal haemorrhage	4.0	5.3
Endometrial hyperplasia‡	<0.1	0.9
Uterine polyp‡	0.4	1.8
Uterine polypectomy	0.2	0.8
Investigations		
Weight increased	5.7.	6.1
Metabolism and nutrition		
Hypercholesterolaemia‡	3.7	2.1
Musculoskeletal		
Arthralgia‡	17.6	10.8
Back pain	9.3	7.7
Pain in limb	6.4	4.7
Osteoarthritis‡	6.1	4.7
Osteoporosis	5.2	2.9
Muscle cramp‡	1.4	3.2
Nervous system		
Headache[3]	13.6	11.2
Dizziness[3]	10.0	8.8
Paraesthesia‡	2.8	1.0
Carpal tunnel syndrome‡	2.8	0.2
Neuropathy‡	0.5	<0.1
Psychiatric		
Insomnia‡	12.9	9.0
Depression	6.2	5.6
Skin & subcutaneous tissue disorders		
Hyperhidrosis[3]	12.0	10.6

‡ Indicates a significant difference at 1% level.

[1] Graded according to Common Toxicity Criteria.

[2] 75 patients received tamoxifen 30 mg daily.

[3] Event actively sought.

The incidence of myocardial infarction (0.6% vs 0.2%, p=0.030) and cardiac failure (1.1% versus 0.7%, p=0.123) in patients treated with AROMASIN compared with those treated with tamoxifen was not significant at the nominal significance level of 0.01 used to allow for multiple testing.

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.

Musculoskeletal and connective tissue disorders

Trigger finger, tenosynovitis stenosans. Tendonitis, tenosynovitis, tendon rupture have been reported in association with third generation aromatase inhibitors.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

Clinical trials have been conducted with AROMASIN 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 AROMASIN that could result in life-threatening symptoms is not known.

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 AROMASIN due to extensive protein binding.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. In postmenopausal women, estrogens are produced primarily from the conversion of androgens into estrogens through the aromatase enzyme in peripheral tissues.

Estrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, AROMASIN significantly lowered serum estrogen 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 estrogenic 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 reduction in estrogen levels stimulating pituitary secretion of gonadotropins. A dose-related decrease in SHBG was observed, which occurred with exemestane 25 mg/day.

A sub-study of endometrial thickness was done in the early breast cancer trial 031 in patients who had received 2-3 years of tamoxifen treatment. The sub-study contained 113 patients, 61 of whom received exemestane and 52 continued on tamoxifen. At baseline, 64% of exemestane patients and 63% of tamoxifen patients had abnormal endometrial thickening ($\geqslant$5 mm on ultrasound). After 2 years, the proportion of exemestane patients with abnormal endometrial thickening had decreased to 36% whereas the proportion of tamoxifen patients with abnormal endometrial thickening remained near baseline at 64%. The difference between treatments after adjusting for baseline was statistically significant (p=0.0025).

Clinical trials

Sequential adjuvant treatment of early breast cancer

In a multicentre, randomised, double-blind study (number 031), conducted in 4724 postmenopausal patients with estrogen receptor-positive or unknown primary breast cancer, patients who had remained disease-free after receiving adjuvant tamoxifen therapy for 23 years were randomised to receive 2-3 years of AROMASIN (25 mg/day) or tamoxifen (20 or 30 mg/day) to complete a total of 5 years of hormonal therapy.

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 AROMASIN after 2-3 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 (Table 2, Figure 1).

Results showed that in the observed study period AROMASIN 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. Statistical significance

was not maintained in a few sub-groups with small sample sizes. These showed a trend favouring exemestane in patients with more than 9 nodes positive, or previous chemotherapy CMF. In patients with nodal status unknown, previous chemotherapy other, as well as unknown/missing status of previous hormonal therapy a non statistically significant trend favouring tamoxifen was observed.

In addition, exemestane 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).

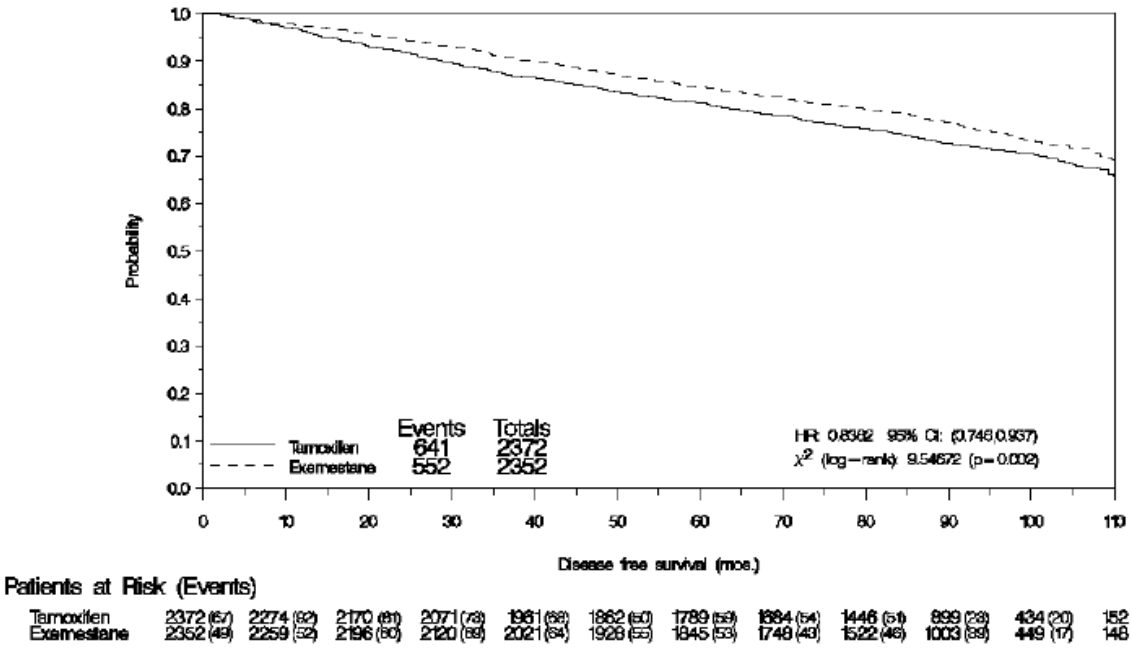
AROMASIN also reduced the risk of contralateral breast cancer, although the effect was no longer statistically significant in this observed study period (hazard ratio 0.74, p=0.12983). In the whole study population, a trend for improved overall survival was observed for exemestane (373 deaths) compared 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 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.

Results from a bone sub-study indicate that treatment with exemestane for 2-3 years following 2-3 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).

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

Figure 1. Disease-free survival in study 031 of postmenopausal women with early breast cancer



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

AROMASIN 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). AROMASIN 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 AROMASIN 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 AROMASIN 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 AROMASIN compared with tamoxifen when adjusting for the prespecified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients compared with tamoxifen only-treated patients (9.9% vs. 12.4%).

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

Table 2. Efficacy results from IES in postmenopausal women with early breast cancer (ITT)

	No. of Events		**Hazard Ratio**	
	Exemestane	**Tamoxifen**	**Hazard Ratio**	**p-value**
30-Month Median Treatment and 34.5-Month Median Follow-Up				
Disease-free survival[a]	213	306	0.69 (95% CI: 0.58-0.82)	0.00003
Breast cancer-free survival[b]	171	262	0.65 (95% CI: 0.54-0.79)	<0.00001
Contralateral breast cancer	8	25	0.32 (95% CI: 0.15-0.72)	0.00340
Distant recurrence-free survival[c]	142	204	0.70 (95% CI: 0.56-0.86)	0.00083
Overall survival[d]	116	137	0.86 (95% CI: 0.67-1.10)	0.22962
30-Month Median Treatment and 52-Month Median Follow-Up				
Disease-free survival[a]	354	453	0.77 (95% CI: 0.67-0.88)	0.00015
Breast cancer-free survival[b]	289	373	0.76 (95% CI: 0.65-0.89)	0.00041
Contralateral breast cancer	20	35	0.57 (95% CI: 0.33-0.99)	0.04158
Distant recurrence-free survival[c]	248	297	0.83 (95% CI: 0.70-0.98)	0.02621
Overall survival[d]	222	262	0.85 (95% CI: 0.71-1.02)	0.07362
30-Month Median Treatment and 87-Month Median Follow-Up				
Disease-free survival[a]	552	641	0.84 (95% CI: 0.75-0.94)	0.002
Breast cancer-free survival[b]	434	513	0.82 (95% CI: 0.72-0.94)	0.00263
Contralateral breast cancer	43	58	0.74 (95% CI: 0.50-1.10)	0.12983
Distant recurrence-free survival[c]	353	409	0.85 ((95% CI: 0.74-0.98)	0.02425
Overall survival[d]	373	420	0.89 (95% CI: 0.77-1.02)	0.08972
30-Month Median Treatment and 119-Month Median Follow-Up				
Disease-free survival[a]	672	761	0.86 (95% CI: 0.77-0.95)	0.00393

Table 2. Efficacy results from IES in postmenopausal women with early breast cancer (ITT)

	No. of Events		Hazard Ratio	
	Exemestane	**Tamoxifen**	**Hazard Ratio**	**p-value**
Breast cancer-free survival[b]	517	608	0.83 (95% CI: 0.74-0.93)	0.00152
Contralateral breast cancer	57	75	0.75 (95% CI: 0.53-1.06)	0.10707
Distant recurrence-free survival[c]	411	472	0.86 (95% CI: 0.75-0.98)	0.02213
Overall survival[d]	467	510	0.91 (95% CI: 0.81-1.04)	0.15737

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

a. Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or death from any cause.
b. Breast cancer-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or breast cancer death.
c. Distant recurrence-free survival is defined as the first occurrence of distant recurrence or breast cancer death.
d. Overall survival is defined as occurrence of death from any cause.

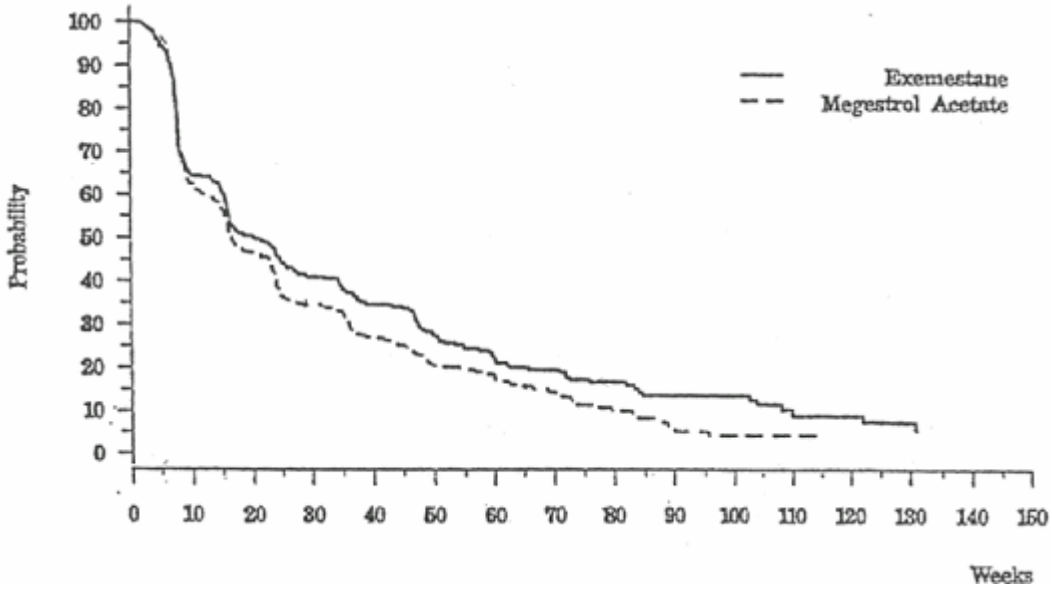
Treatment of advanced breast cancer

Efficacy data in patients progressing while on anti-estrogen therapy (second-line treatment) include results from a phase III study (multicentre, multinational, peer-reviewed, randomised, double-blind, controlled) with AROMASIN 25 mg daily versus megestrol acetate 40 mg 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 estrogen 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 AROMASIN and megestrol acetate are equivalent in terms of objective responses, with objective response rates of 12.4% for megestrol acetate versus 15.0% for AROMASIN (C.I. for difference -7.5+2.3). Overall success rates (Complete Response, Partial Response or No Change) are also comparable, 37.4% for AROMASIN 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 AROMASIN-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 AROMASIN 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 AROMASIN 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 AROMASIN. In the combined analysis, which was of the descriptive type, AROMASIN 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). AROMASIN 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.

Metabolism and excretion

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 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 Insufficiency: Exemestane pharmacokinetics has been investigated in subjects with severe renal insufficiency (CL_{CR} ≤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, AROMASIN should be used with caution in patients with renal insufficiency.

Hepatic Insufficiency: 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, AROMASIN should be used with caution in patients with hepatic impairment.

5.3 Preclinical safety data

Genotoxicity

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 at doses ≥50 mg/kg/day in males and ≥150 mg/kg/day in females. Exposures (plasma AUC) at these doses were 4 and 37 times, respectively, exposure in patients at the recommended dose. However, statistical significance was only reached at the high dose exposures (approximately 34 (male) and 75 (female) fold the AUC in patients). An increased incidence of renal tubular adenomas was observed in male mice at the high dose of 450 mg/kg/day.

A 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. At the highest dose, plasma $AUC_{(0\text{-}24hr)}$

levels in male and female rats were 19 and 31 fold higher than those measured in the postmenopausal cancer patients, receiving the recommended clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal hydrated silica,
Crospovidone,
Hypromellose,
Magnesium carbonate hydrate,
Magnesium stearate,
Mannitol,
Microcrystalline cellulose,
Methyl hydroxybenzoate,
Macrogol 6000,
Polysorbate 80,
Polyvinyl alcohol,
Simethicone,
Sodium starch glycollate,
Sucrose,
Titanium dioxide,
Cetyl esters wax,
Purified talc,
Carnauba wax,
Black printing ink.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

25 mg tablets in blister packs: 15s, 30s, 90s.

Not all pack sizes may be marketed.

6.6 Special conditions for disposal

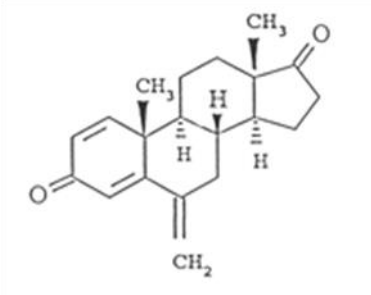
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Non-proprietary name: Exemestane

Chemical name: 6-methylenandrosta-1,4-diene-3,17-dione



Exemestane is a white or yellowish-white powder, which is freely soluble in N,N-dimethylformamide, soluble in methanol and practically insoluble in water. Due to the very low solubility in water, the drug is micronised.

CAS number

CAS-107868-30-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedinfo.com.au

9. DATE OF FIRST APPROVAL

30 November 2000

10. DATE OF REVISION

12 July 2024

® AROMASIN is a registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	**Tendon disorders** The use of third generation aromatase inhibitors, including exemestane, were found to be associated with tendonitis and tenosynovitis in randomised controlled trials. Tendon rupture was found to be a potential risk associated with third generation aromatase inhibitors. Monitor patients for signs and symptoms of tendon disorders during treatment with AROMASIN.
4.8	Addition of "tendonitis, tenosynovitis, tendon rupture" as post-marketing ADRs.