HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 July 2006

Aromasin[1] 25 mg, film-coated tablets
Box of 30 tablets: 352 796-6

Exemestane

Applicant: Pfizer

List I

Date of Marketing Authorisation: 19 November 1999
Marketing Authorisation (AMM) amended on 13 December 2005 (extension of indication)

Reason for request: modification of listing conditions.
Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication
"Aromasin is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy".

Exemestane (Aromasin) is now indicated as adjuvant hormonal therapy for oestrogen receptor-positive early invasive breast cancer in a sequential regimen combining tamoxifen followed by Aromasin. Sequential therapy has been more effective in patients successfully treated for 2–3 years with tamoxifen than tamoxifen therapy for 5 years. The two treatment strategies have different safety profiles.

Current clinical data are insufficient to determine how sequential therapy stands compared to aromatase inhibitors for 5 years or tamoxifen for 5 years followed by letrozole (Femara).

Health Technology Assessment Division

[1] Aromasine in French

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Exemestane

1.2. Indications

- Aromasin is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy **(extension of indication).**

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

Efficacy has not been demonstrated in patients with oestrogen receptor negative status.

1.3. Dosage

- Adults and the elderly

The recommended dose of Aromasin is one 25 mg tablet taken once daily, preferably after a meal. Aromasin therapy should continue until there are signs of tumour progression.

In patients with early breast cancer, treatment with Aromasin® should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Aromasin). Treatment should be stopped if tumour recurrence occurs.

In patients with advanced breast cancer, treatment with Aromasin should continue until there are signs of tumour progression.

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

- Children: Aromasin should not be used in children.

2 SIMILAR MEDICINAL PRODUCTS

2.1. 2005 ATC Classification

L : Antineoplastic and immunomodulating agents
L02 : ENDOCRINE THERAPY
L02B : HORMONE ANTAGONISTS AND RELATED AGENTS
L02BG : ENZYME INHIBITORS
L02BG06 : Exemestane[2]

[2] Exemestane is an irreversible specific steroidal aromatase inhibitor.

2.2. Medicines in the same therapeutic category

2.2.1. Comparator drugs

Other aromatase inhibitors:

- anastrozole (Arimidex 1 mg, tablets).

Indicated in the treatment of hormone receptor positive breast cancer in postmenopausal women, as adjuvant therapy.

- letrozole (Femara 2.5 mg, tablets)

Indicated in postmenopausal women who have previously received standard adjuvant therapy with tamoxifen for 5 years, as extension of adjuvant therapy for early-stage breast cancer (for a period of at least 2 years).

2.3. Medicines with the same therapeutic aim

- Tamoxifen: Nolvadex 10 mg and 20 mg and generic versions.
- Cytotoxics with an indication for adjuvant therapy.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The extension of indication of exemestane (Aromasin) in the adjuvant therapy of early-stage invasive breast cancer is based on the results of a clinical trial (the Intergroup Exemestane Study (IES) trial) carried out in postmenopausal women with oestrogen-receptor positive (OR+), histologically confirmed, completely resected unilateral invasive breast cancer.

After taking tamoxifen for 2 or 3 years, the aim of this trial was to compare the efficacy and safety of two treatment options for continuing treatment:

- either replacing tamoxifen with exemestane 25 mg/day,
- or continuing with tamoxifen (at a dose of 20–30 mg/day),

for 5 years of hormone therapy (in accordance with the duration recommended in clinical practice guidelines).

Methodology

Phase III comparative randomised double-blind trial. Patients had to have received adequate therapy for the primary cancer, including postoperative radiotherapy in the event of breast-conserving surgery. Patients could have received neoadjuvant chemotherapy.

The primary efficacy endpoint was disease-free survival (DFS)[3].

Secondary endpoints were overall survival, the incidence of contralateral breast cancer, and long-safety.

The protocol was also designed to assess the impact of treatment on quality of life, uterine thickness, bone mineral density and incidence of bone fractures.

[3] For subjects who had experienced an event, disease-free survival was defined as the time from randomisation to recurrence of breast cancer at any site (local or distant recurrence), diagnosis of a second primary breast cancer, or death from any cause. For subjects who had had no events at the date of the last record, it was the time from the date of randomisation to the date of last record. For each patient, only the first event was taken into account in the calculation of disease-free survival.

Results

Note: The results of the IES trial were published as a full paper[4] after a median follow-up of 30.6 months, then as an abstract[5] during the American Society of Clinical Oncology 2006 conference after a median follow-up of 55.7 months.

Patient characteristics

The efficacy analysis concerned 2352 patients in the exemestane group and 2372 patients in the tamoxifen group. The median age of patients was 64 years. The nodal status was positive at the time of diagnosis in 44% of patients in both groups. Overall, 56 patients (2.4%) in the exemestane group and 66 patients (2.8%) in the tamoxifen group were hormone receptor negative. Approximately 85% of patients were OR+.

Results after approximately 34.5 months of follow-up

Primary efficacy endpoint: 213 events corresponding to the primary endpoint were reported in the exemestane group and 306 in the tamoxifen group. There was a 31% reduction in disease-free survival in the exemestane group compared with the tamoxifen group (RR = 0.69; $p<0.00003$) in favour of sequential therapy. This effect was observed in OR+ patients.

Estimated disease-free survival at 3 years was 90% in the exemestane group and 86% in the tamoxifen group (by the Kaplan-Meier method).

Secondary endpoints: survival without distant recurrence was improved in the exemestane group compared with tamoxifen group (RR = 0.70, $p<10^{-2}$).

Results after median follow-up of 55.7 months

- 354 primary endpoint events were reported in the exemestane group and 450 for the tamoxifen group, i.e. a reduction of 24% in onset of a primary endpoint event (local or regional recurrence, distant recurrence, second primary breast cancer or death from any cause) in the exemestane group compared with the tamoxifen group (RR = 0.76; p=0.0001).

- 222 patients died in the exemestane group and 261 in the tamoxifen group. Overall survival increased slightly for patients who had received tamoxifen for 2–3 years followed by Aromasin (RR 0.85; p=0.08) compared with those who had received tamoxifen for 5 years.

Substudy of quality of life

Quality of life of patients in the IES trial was assessed using the FACT-B questionnaire (Functional Assessment of Cancer Therapy-Breast) and the ES scale (Endocrine Subscale). The primary endpoint was the TOI Index (Trial Outcome Index) obtained by summing the scores for different items on the FACT-B scale.

This assessment concerned 582 patients, with a response level of about 85% for all follow-up questionnaires. The results have been published[6]. During a 2 year follow-up period, there was no difference between the two study groups in terms of quality of life.

Other data submitted by the company

An indirect comparison of aromatase inhibitors in sequential adjuvant therapy for breast cancer in hormone-receptor positive postmenopausal women

[4] Coombes RC et al. Intergroup Exemestane study. A Randomized Trial of Exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-92.
[5] ASCO, 42nd Annual Meeting: abstract LBA 527. Presented June 5, 2006.
[6] Fallowfield LJ et al Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. J Clin Oncol. 2006;24:910-7.

Four phase III trials assessed the efficacy of aromatase inhibitors in adjuvant therapy for breast cancer after 2–3 years of hormone therapy with tamoxifen: the IES trial, the ABCSG 8 and ARNO 95 trials[7] and the ITA trial[8].

Methodology and patients in the IES, ABCSG 8/ARNO 9 and ITA trials

		IES	ABCSG 8/ARNO 9	ITA
Methodology	N	4724	3123	448
	Trial design	Randomised multicentre double-blind trial	**2 pooled** randomised multicentre open trials	Single centre randomised open trial
	Primary endpoint	DFS = Local and distant recurrence, contralateral cancer and death	EFS = Local or distant recurrence, contralateral cancer	RFS = Local or distant recurrence
	Treatments compared	Exemestane (Aromasin®) vs. Tamoxifen after 2–3 years of tamoxifen	Anastrozole vs. Tamoxifen after 2–3 years of tamoxifen	Anastrozole vs. Tamoxifen after 2–3 years of tamoxifen
Patients:	Treatment completed (% patients)	90	55	Not reported
	Lymph node invasion (%)	48	27	100
	Previous chemotherapy (%)	32	0	67

Clinical results for IES, ABCSG 8/ARNO 9 and ITA trials

		IES		ABCSG 8/ARNO 9		ITA	
	Follow-up (months)	36		28		36	
Efficacy	Disease-free survival = DFS						
	RR	0.69					
	p	0.00003					
	Absolute gain	3.8%					
	Breast cancer-free survival = EFS						
	RR	0.65		0.59			
	p	< 0.00001		0.0008			
	Absolute gain	3.8%		3.1%			
	Distant recurrence-free survival						
	RR	0.70		0.54		0.49	
	p	0.0008		0.002		0.06 (NS)	
	Absolute gain	2.6%		NR		NR	
	Overall survival						
	RR	0.86		NR			
	p	0.23		0.16			
	Absolute gain	0.8%		1%			
Side effects:		EXE	TAM	ANA	TAM	ANA	TAM
	Dyslipidaemia (%)	3.5 ^{S}	1.9	NR	NR	9.3 ^{S}	4.0
	Fractures	NS	NS	2 ^{S}	1	NS	NS
	Osteoporosis (%)	5.2 ^{S}	2.9	NR	NR	NR	NR
	Gastrointestinal side-effects (%)	4.4 ^{S*}	2.2	2 ^{S**}	<1	7.9 ^{S}	2.7
	Thromboembolic events (%)	0.7	1.8 ^{S}	0.3	1.3 ^{S}	NR	NR

*^{S} difference significant; * Diarrhoea; ** Nausea; NR=Not reported; NS=Not significant*
EXE = exemestane; TAM = tamoxifen; ANA = anastrozole

The populations studied were not comparable, particularly in terms of hormone receptor status and lymph node involvement. Definitions of events differed among trials. With regard to safety, there were differences in the definitions of undesirable events, the assessment scales used, and the procedure specified for detecting each event. It is therefore not possible to compare the results of these trials.

[7] Jakesz R et al. ABCSG and the GABG. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. 2005;366:455-62.

[8] Boccardo F et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 2005;23:5138-47.

The results of an ongoing comparative trial (BIG 1-98) should help determine the contribution of sequential therapy compared with the other treatment options, including the option of prescribing an aromatase inhibitor for 5 years.

3.2. Adverse effects

Adverse effects were recorded in 4531 patients in the IES trial, 2252 in the exemestane group and 2279 in the tamoxifen group, over a median follow-up of about 40 months (3 years). Adverse effects were reported in 73.1% of patients.

The treatment discontinuation rate because of adverse effects was 6.3% (148 patients) in the exemestane group and 5.2% (124 patients) in the tamoxifen group.

The most common adverse effects were hot flushes (22%), arthralgia (17%) and tiredness (17%).

Serious adverse effects were classified as related to treatment in 2.6% of patients treated with exemestane and in 3.9% of patients treated with tamoxifen.

The number of deaths from any cause occurring during the treatment period or within 30 days of discontinuing treatment was the same (about 1.5%).in both groups.

Compared with tamoxifen, exemestane was associated with a higher incidence of arthralgia, insomnia, osteoporosis and, less frequently, diarrhoea, hypercholesterolaemia, paraesthesia, carpal tunnel syndrome, gastric ulcers, and neuropathy. Tamoxifen was associated with a higher incidence of muscle cramp, uterine polyps, endometrial hyperplasia and deep vein thrombosis.

The number of patients experiencing a second primary cancer, excluding a cancer of the breast, was higher in the tamoxifen group (86) than in the exemestane group (55). The most common cancers were uterine cancer and lung cancer, which occurred in both groups. Their incidence was, however, two-fold higher in patients treated with tamoxifen (14 versus 6 and 13 versus 6, respectively). Basal cell carcinoma was reported in 10 patients treated with tamoxifen and 5 patients treated with exemestane.

After 30 months' follow-up, the incidence of fractures was the same in the global population of the IES trial, whether patients received exemestane (3.8%) or tamoxifen (2.7%). The impact of exemestane (Aromasin) on long-term fracture risk was therefore not demonstrated[9]. However, after a median follow-up of nearly 55 months, a higher number of fractures was observed in patients who had received exemestane (7.0%) than in those who had continued treatment with tamoxifen (4.9%), $p = 0.003$.

In view of the available clinical data on efficacy and safety, it has not been established that the impact of exemestane on cardiovascular risk is different from that of tamoxifen or other aromatase inhibitors.

3.3. Conclusion

The Intergroup Exemestane Study (IES) assessed, in 4724 postmenopausal patients who had been successfully treated with tamoxifen 20–30 mg/day for 2–3 years for hormone receptor positive or hormone receptor unknown early breast cancer, the efficacy and safety of two treatment options, i.e. exemestane 25 mg/day or continued treatment with tamoxifen 20–30 mg/day to give a total duration of adjuvant hormone therapy of 5 years.

[9] According to the SPC for the product, "treatment for osteoporosis should be initiated as appropriate" and "women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry".

After a median treatment period of 37 months and median follow-up of 35 months, the improvement in DFS was greater with tamoxifen followed by exemestane than with tamoxifen (RR = 0.69; p < 0.001). The risk of contralateral breast cancer was also further reduced with exemestane than tamoxifen (RR = 0.32; p = 0.034) and led to reduced mortality after a median follow-up of nearly 56 months. This absolute benefit in mortality was modest (difference between the groups not significant). After a follow-up period of 2 years, there was no difference in terms of quality of life between the patient groups.

The design of the IES trial excluded patients with "early recurrence" on tamoxifen. The contribution of sequential therapy compared with 5 years of tamoxifen treatment has therefore not been established in these patients.

There are no clinical data to determine the benefit of sequential treatment compared with treatment with an aromatase inhibitor prescribed immediately. However, this is currently the option most often chosen by oncologists (See Transparency Committee Opinion of 19 May 2004 on Arimidex, in particular; see experts' opinion).

The most common undesirable effects with exemestane were hot flushes (22%), arthralgia (17%) and tiredness (17%).

After 30 months' follow-up, the incidence of fractures was similar, whether patients received exemestane (3.8%) or tamoxifen (2.7%). However, after a median follow-up of nearly 55 months, a higher number of fractures was observed in patients who had received exemestane than in those who had continued treatment with tamoxifen.

Note: The preliminary results of the substudy assessing the impact of both treatments on the endometrium showed a median decrease in endometrial thickness of 28.6% (52 patients) with exemestane and 5.3% (51 patients) with tamoxifen after 2 years of treatment. Endometrial thickening, reported at the start of the trial, returned to less than 5 mm for 50% of patients taking exemestane (See SPC)

4 TRANSPARENCY COMMITTEE CONCLUSIONS

Aromasin is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

4.1. Actual benefit

Breast cancer is a serious and common life-threatening disease (incidence doubled in 20 years, 32 000 new cases in women over 50 in the year 2000).

As adjuvant therapy for oestrogen receptor positive invasive early breast cancer following initial adjuvant therapy with tamoxifen for 2–3 years, Aromasin is first-line therapy. Aromasin is intended as curative therapy.

Public health benefit:
Localised breast cancer is a major public health burden.
The introduction of new treatment methods for localised breast cancer is a public health need. It is one of the GTNDO objectives for cancer.
According to current clinical data for patients successfully treated with tamoxifen for 2–3 years, replacing tamoxifen with exemestane (Aromasin) improves morbidity and mortality.
Aromasin should therefore partially cover the identified public health need.
Consequently, in the current state of knowledge, Aromasin given after 2–3 years of tamoxifen has an anticipated public health benefit. This benefit is small and temporary as the number of patients treated from the outset is decreasing.

The efficacy/adverse effects ratio for exemestane is high.
There are alternative drugs, i.e. anastrozole (Arimidex) prescribed from the outset and tamoxifen for 5 years followed by letrozole (Femara).

The actual benefit of Aromasin is substantial.

4.2. Improvement in actual benefit:

According to the IES trial results, sequential therapy [tamoxifen followed by Aromasin (exemestane)] compared to tamoxifen provides a moderate improvement in actual benefit (IAB level III) in terms of efficacy when adjuvant hormone therapy is prescribed for 5 years to postmenopausal women with oestrogen receptor positive early breast cancer. Its prescription is therefore justified in patients who have received adjuvant therapy with tamoxifen for 2–3 years.

2.1 Therapeutic use

In localised oestrogen and/or progesterone-receptor positive breast cancer, standard adjuvant therapy includes hormone therapy with tamoxifen, in most cases given after chemotherapy.

The superiority of an aromatase inhibitor (anastrozole) over tamoxifen has been demonstrated in a comparative trial in postmenopausal women (ATAC trial[10]).

The accepted duration of hormone therapy based on trials of adjuvant therapy with tamoxifen is 5 years[11]. Longer treatment seems to be associated with a higher frequency of thromboembolic events and of endometrial cancer.[12] [13]

Aromasin is now indicated (extension of indication) in postmenopausal women as adjuvant therapy for early invasive oestrogen-receptor positive breast cancer. Clinical benefit is expected when it is prescribed after adjuvant tamoxifen therapy for 2–3 years and compared with continuing treatment with tamoxifen. It should be noted that the proportion of patients who have received 2–3 years of tamoxifen is currently decreasing because of the increased use of aromatase inhibitors as first-line therapy.

A trial[14] comparing sequential therapy with anastrozole administered after two years of tamoxifen with tamoxifen therapy for 5 years reported a significant 40% reduction in the relative risk of an event. This corresponding to an improvement in DFS with anastrozole of 3.1% at 3 years.

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[10] Baum M et al Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer. 2003;98:1802-10

[11] Fischer B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.J. Natl Cancer Inst 2001; 93: 684-90

[12] Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–717

[13] Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: twenty-eight years later. J Clin Oncol 1995;13:513–29

[14] Jakesz R et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005; 366:455-62.

These data suggest the benefit of sequential adjuvant therapy with tamoxifen for 2–3 years followed by an aromatase inhibitor. Nevertheless, as there are no comparative trials, it is not yet possible to determine the benefit of sequential therapy compared with the use of an aromatase inhibitor for 5 years (which is currently the treatment most commonly prescribed as 1st-line therapy). Letrozole (Femara) 2.5 mg also has an indication in patients who have received 5 years of tamoxifen.

Target population

In 2000, the number of incident cases of breast cancer was 42 000[15]. The number of cases in postmenopausal women may be established from the number of cases affecting women aged over 50, i.e. 32 000. As the mean annual rate of growth in breast cancer incidence is 2.4%, it can be estimated that the number of incident cases of breast cancer in postmenopausal women in 2004 was 35 000.

Given that:

- 5%–15% of women[16] have metastatic disease when first diagnosed, it may be estimated that 85–95% of women with breast cancer have an indication for adjuvant therapy (excluding advanced stage disease) after locoregional therapy,

- the mean percentage of women with hormone receptor positive cancer (RH+) is about 80%[17,18],

the estimated number of postmenopausal women with HR+ breast cancer who could benefit from adjuvant therapy is 23 800–26 600.

Note: According to the company's estimates (and using the hypothesis that the mean duration of tamoxifen treatment is 2.5 years), about 23 000 patients in 2006 had taken tamoxifen for 2–3 years and were eligible for treatment with Aromasin.

The proportion of patients receiving adjuvant tamoxifen therapy for 5 years has been estimated to be 60%.[19,20] (see Opinion of 19 October 2005 on Femara)

The target population for Aromasin in its extended indication may be determined from the population corresponding to the cohort of patients who started treatment with tamoxifen in 2004 (2 years of treatment with tamoxifen. This is about 14 000–16 000 patients a year but is probably an overestimate as it does not take into account:

1- the proportion of patients who discontinued tamoxifen between 2.5 and 5 years, which is unknown;

2- especially, **the anticipated decrease in the number of patients who have received 2–3 years of tamoxifen because of the increased use of aromatase inhibitors as first-line therapy.** This change in practice seems to be confirmed by a study of prescriptions and by the results of a market study of hormone therapy in France carried out on behalf of pharmaceutical companies concerned by adjuvant hormone therapy in breast cancer.

[15] Change in incidence of and mortality from cancer in France between 1978 and 2002 (INVS, October 2003)

[16] Francim/ FNCLCC survey

[17] Mann GB et al. Reliance on hormone receptor assays of surgical specimens may compromise outcome in patients with breast cancer. J Clin Oncol. 2005;23:5148-54.

[18] Colozza M, Larsimont D, Piccart MJ. Progesterone receptor testing: not the right time to be buried. J Clin Oncol. 2005;23:3867-8.

[19] Sacco M et al. Randomized trial of 2 Versus 5 years of adjuvant tamoxifen for women aged 50 years or older With early breast cancer: Italian Interdisciplinary Group for Cancer Evaluation Study of Adjuvant Treatment in Breast Cancer 01. J Clin Oncol 2003; 2:2276-81

[20] Baum M et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer. American Cancer Society 2003

2.3 Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication

4.2.1. Packaging: Appropriate for the prescription conditions

4.2.2. Reimbursement rate: 100%