Pharmacoeconomic analysis of adjuvant therapy with exemestane, anastrozole, letrozole or tamoxifen in postmenopausal women with operable and estrogen receptor-positive breast cancer

Juan Miguel Gil[a], Carlos Rubio-Terrés[b], Almudena del Castillo[c], Paloma González[c] and Felisa Canorea[c]

[a]Oncology Unit-Unidad Funcional de Mama. Institut Català d'Oncología. L'Hospitalet. Barcelona. Spain. [b]HERO Consulting. Health Economics and Research of Outcomes. Madrid. Spain. [c]Medical Unit. Pfizer I+D+i. Pfizer España. Madrid. Spain.

Objective. **To compare the efficiency of adjuvant therapy with aromatase inhibitors or with tamoxifen in postmenopausal women with operable breast cancer and positive estrogen receptors.**

Material and methods. **A cost-utility analysis was performed based on a Markov model, from the Spanish National Health Care System perspective, comparing the treatment with exemestane (EXE: 25 mg/day) or tamoxifen (TAM: 20 mg/day) after 2-3 years of monotherapy with TAM; anastrozole (ANA, 1 mg/day) or TAM (20 mg/day) without previous TAM therapy; and letrozole (LET: 2.5 mg/day) or placebo after 5 years of monotherapy with TAM. The follow-up of a hypothetical cohort of women starting treatment at 63 years of age was simulated during 10 and 20 years. The probabilities of transition between health states and quality adjusted life years (QALYs) were obtained from the literature, and the unit costs (€ corresponding to 2004) from a Spanish database.**

Results. **After 10 and 20 years of follow-up, more QALYs per patient would be gained with the EXE scheme (0.230-0.286 and 0.566-0.708, respectively) than with ANA (0.114 and 0.285) and LET (0.176 and 0.474). The cost of gaining one QALY was lower with the EXE scheme (50,801-62,522 € and 28,849-35,371 €, respectively) than with ANA (104,272 € and 62,477 €) and LET (91,210 € and 49,460 €). The result was stable for the cost per life-year gained (LYG) and in the sensitivity analysis.**

Conclusions. **The EXE scheme after TAM is more cost-effective than the ANA and LET schemes.**

Key words: exemestane, tamoxifen, anastrozole, letrozole, breast cancer, cost-utility, cost-effectiveness, life-year gained (LYG), quality adjusted life year (QALY).

Gil JM, Rubio-Terrés C, del Castillo A, González P, Canorea F. Pharmacoeconomic analysis of adjuvant therapy with exemestane, anastrozole, letrozole or tamoxifen in postmenopausal women with operable and estrogen receptor-positive breast cancer. Clin Transl Oncol. 2006;8(5):339-48.

INTRODUCTION

Breast cancer (BC) is the most common neoplastic process in women, representing 28% of all cancers[1]. BC is estrogen-dependent in many cases, as a result of which a reduction in estrogen levels may give rise to disease regression - particularly in tumors characterized by a marked over-expression of estrogen receptors[2,3]. Tamoxifen (TAM) is an antiestrogen drug that when administered as adjuvant therapy during 5 years to women with operable BC (OBC) and positive estrogen receptors, reduces recurrence, giving rise to a reduction in annual mortality of 31% after 15 years of follow-up[4].

Aromatase is an enzyme that catalyzes the conversion of androgens to estrogens - this represents the main source of estrogens in postmenopausal women. At present, two types of third-generation aromatase inhibitors (AIs) are available: steroids, such as exemestane (EXE), which produces an irreversible inhibition of the enzyme; and the non-steroids such as anastrozole (ANA) and letrozole (LET), which induce a reversible enzyme inhibition[5]. AIs have been shown to be more effective than TAM in the OBC treatment, affording superior disease-free survival in three randomized clinical megatrials comparing EXE and

Correspondence: A. del Castillo-Saiz.
Pharmacoeconomic and Health Outcomes Research Departament.
Unidad Médica, Pfizer S.A.
Parque Empresarial «La Moraleja».
Avda. de Europa, 20-B.
28108 Alcobendas, Madrid. Spain.
E-mail: almudena.delcastillo@pfizer.com

Received 6 September 2005; Accepted 22 November 2005.

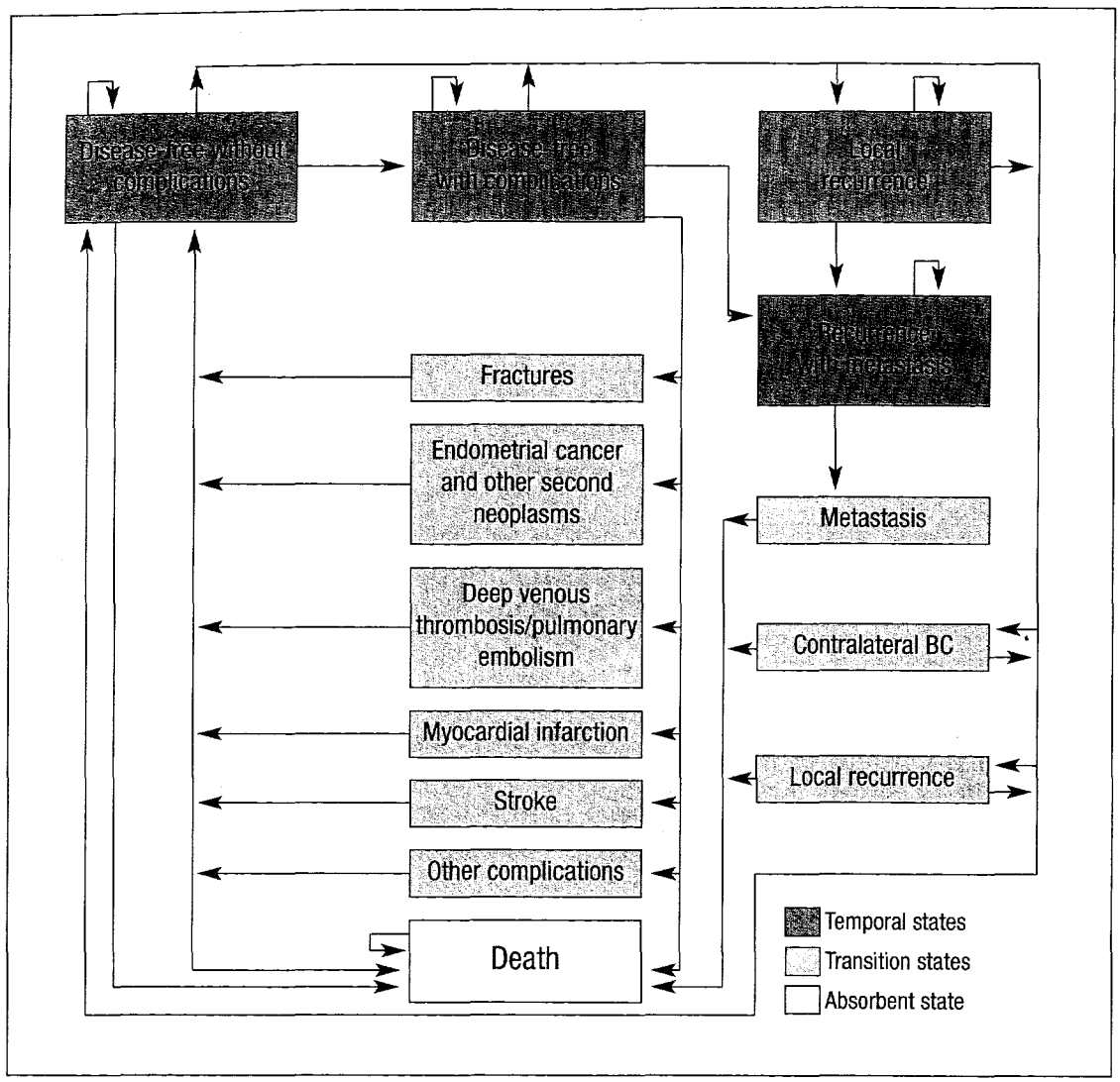

Fig. 1. Markov model of operable breast cancer in postmenopausal women with positive estrogen receptors.

TAM after 2-3 years of monotherapy with TAM (IES study)[6,7], ANA and TAM without prior treatment with TAM (ATAC study)[8], and LET with placebo (PBO) after 5 years of monotherapy with TAM (MA17 study)[9].

It has been estimated that the cost of local recurrence of breast cancer is about 6,300 €, while the cost of a second contralateral BC is approximately 5,600 €, and a case of metastasis due to BC costs about 10,000 €[10]. On the other hand, the cost of treatment with AIs is far greater than the cost of treatment with TAM[11]. The importance of these figures, and the socioeconomic impacts of BC, justify the conduction of model-based pharmacoeconomic analyses to assess the efficiency of the different available treatments.

The purpose of the present study is to evaluate and compare the cost-utility ratio of oral adjuvant therapy in postmenopausal women with OBC and positive estrogen receptors, based on the following oral administration schemes: 1) EXE (25 mg/day) or TAM (20 mg/day) after 2-3 years of monotherapy with TAM; 2) ANA (1 mg/day) or TAM (20 mg/day) without prior treatment with TAM; and 3) LET (2.5 mg/day) or PBO, after 5 years of monotherapy with TAM.

METHODS

Pharmacoeconomic model

The study comprised a pharmacoeconomic model, defined as a theoretical scheme that allows making simulations of complex drug-related health care processes, and elaborated on the basis of a previously established protocol involving estimations obtained from the available data (published or otherwise) relating to efficacy, toxicity and costs of the compared alternatives[12]. A Markov model was used[13], with the structure shown in figure 1, and which is described

in greater detail further below. Analysis of the Markov model was carried out with *DATA 3.5 for Healthcare* of TreeAge software[14].

Target population

The target population consists of a hypothetical set of patients subjected to theoretical analysis, and therefore represents the population to which the study results can be applied. The target population comprised Spanish postmenopausal women diagnosed with estrogen receptor-positive OBC - the analysis being performed for a hypothetical cohort starting the treatment schemes at 63 years of age, because the mean age of the more than 16,000 patients with OBC who participated in the aforementioned clinical trials was between 62 and 64 years[6-9].

Health states

In accordance to the natural history of OBC, the model considered the following health states: 1) 4 «temporal» states (disease-free without complications, disease-free with complications, local recurrence and metastasis) in which the patients could remain for several one-year cycles; 2) 6 «transition» states (fractures, secondary neoplasms, deep venous thrombosis or pulmonary thromboembolism, myocardial infarction, stroke and other complications) in which the patients could remain for no more than one annual cycle; and 3) a so-called «absorbent» state (patient death) (fig. 1). All the patients in the cohort initially would be disease-free and without complications. In the course of the annual cycles, the patients could remain in that same state or –even if still disease-free –they could experience one or more of the aforementioned complications. At the same time, the patients could suffer local recurrence or develop a contralateral BC, or present metastasis as a consequence of OBC. At any time the patients could die –this being the moment in which the simulation terminates, regardless of whether or not death is attributable to OBC, the complications of therapy, or other causes (fig. 1). The clinical plausibility of the transitions allowed in the model was confirmed by expert oncologists and by other similar pharmacoeconomic models published in the literature[15-17].

Type of study: cost-utility analysis

The type of pharmacoeconomic analysis required depends on whether or not demonstrated differences in efficacy or toxicity exist among the treatments. Consequently, we identified all the comparative clinical trials made with the latter, based on a MEDLINE literature review up until May 2005, the consultation of various recent reviews of the OBC treatment with TAM or AIs (EXE, ANA and LET)[4,5,18-22], and a review of all communications presented at the following oncological congresses: that of the American Society of Clinical Oncology (ASCO)[23], the Annual San Antonio Breast Cancer Symposium[24] and the European Breast Cancer Conference[25], among others.

There are no clinical trials available that directly compare the efficacy of different AIs in application to the present study indication. Tables 1 and 2 summarize the baseline characteristics and results, respectively, of the clinical megatrials (i.e., involving samples of over 1,000 patients) in which comparisons were made of oral adjuvant therapy in women with OBC and positive estrogen receptors based on the following schemes: 1) IES study: in a randomized, double-blind clinical trial, EXE (25 mg/day) or TAM (20 mg/day) was administered after 2-3 years of monotherapy with TAM (N = 4,742 patients; the results obtained with two median follow-up periods are presented: 30.6 and 37.4 months)[6,7]; 2) ATAC study: in a randomized clinical trial, the patients received ANA from the start of the study (1 mg/day) or TAM (20 mg/day) (N = 6,241; follow-up: 33.3 months)[8]; 3) MA17 study: in a randomized, double-blind clinical trial, LET (2.5 mg/day) or PBO was administered, after 5 years of monotherapy with TAM (N = 5,187; follow-up: 28.8 months)[9].

The prognostic factors of the patients included in the three studies (age, lymph node status, pre-randomization therapies, and the percentage of patients with estrogen or progesterone receptors), and the median follow-up were very similar (table 1). Regarding the efficacy results, the patients treated with EXE and ANA yielded longer disease-free survival than those treated with TAM (with statistically significant differences) and, likewise, LET was seen to be more effective than PBO in relation to this parameter. However, none of the AIs has been able to prolong significantly overall survival as yet (table 2).

Since no clinical trials directly compare AIs, it was decided to conduct pharmacoeconomic analyses for each clinical trial, followed by indirect comparisons of the incremental cost-utility results, via application of the following formula:

$$\frac{\text{Costs with EXE or ANA or LET} - \text{Costs with TAM or TAM or PBO}}{\text{Effectiveness or Utilities with EXE or ANA or LET} - \text{Effectiveness or Utilities with TAM or TAM or PBO}}$$

The results are presented as cost per QALY gained (cost-utility) and as cost per life -year gained (LYG) (cost-effectiveness).

Duration of the cycles and time horizon

The transitions among states were made in discrete time periods referred to as «cycles», and which as

TABLE 1. **Baseline characteristics of the patients included in the IES (Exemestane, EXE), ATAC (Anastrozole, ANA) and MA17 studies (Letrozole, LET)**

Characteristics	IES 2004[6]		IES 2005[7]		ATAC 2002[8]		MA17 2003[9]	
	EXE	TAM	EXE	TAM	ANA	TAM	LET	PBO
Number of patients	2,362	2,380	2,352	2,372	3,125	3,116	2,575	2,582
Age, years (SD)	64.3 (8.1)	64.2 (8.2)	63.0	63.0	64.1 (9.0)	64.1 (9.0)	62.4	62.0
Lymph node status (%)								
N+ (1-3)	30.3	29.7	30.7	29.8	24.5	24.4	→46.0[a]	→46.0[a]
N+ (≥ 4)	13.6	13.9	13.9	13.9	10.4	9.1		
Negative	51.3	50.9	51.7	51.8	60.0	61.5	50.0	50.0
Not known	4.8	5.5	3.7	4.5	5.0	4.9	4.0	4.0
Pre-randomization treatments (%)								
Chemotherapy	32.4	32.1	32.9	32.4	22.3	20.8	46.0	46.0
Radiotherapy	NA	NA	NA	NA	63.3	62.5	60.0	59.0
Tamoxifen	100	100	100	100	1.6	1.6	100	100
Years of treatment with Tamoxifen	2.4	2.4	2.4	2.4	–	–	5	5
Positive receptors (%)								
ER and PgR	NA	NA	56.6	55.6	83.7	83.4	98.0	98.0
ER	81.2	81.3	NA	NA	NA	NA	NA	NA
PgR	55.9	55.2	NA	NA	NA	NA	NA	NA

ANA: anastrozole; ATAC: arimidex, tamoxifen alone or in combination; ER: estrogen receptors; EXE: exemestane; IES: intergroup exemestane study; LET: letrozole; NA: information not available in the article of the clinical trial; PBO: placebo; PgR: progesterone receptors; TAM: tamoxifen.
[a]Includes all positive axillary lymph nodes, regardless of number.

previously mentioned had a duration of one year. In a similar way to other OBC pharmacoeconomic models published in the literature[16,17], the time horizon of the simulation was 10 and 20 years from the start of administration of the compared schemes - corresponding in the case of 20 years approximately to the life expectancy of the 63-year-old patients, taking into account that the mean life expectancy among Spanish women is about 83 years[26]. An annual discount of 3.5% was made for the costs and for the benefits (QALY, LYG), according to the recommendations of the National Institute for Clinical Excellence (NICE)[27]. A half-cycle correction was assessed in both cases.

Transition probabilities

Each health state has associated several probabilities of transition (P_t) to the rest of states, benefits or utilities, and costs. The annual rates of the transitions among states were estimated mainly on the basis of the results of the three efficacy clinical trials[6-9]. The annual rates for patient mortality by age and by all causes were obtained from the database of the Spanish National Institute of Statistics (*Instituto Nacional de Estadística, INE*)[28]. Based on the annual rates, calculations were made of the P_t between states, using the formula $P_t = 1\text{-}e^{-rt}$, where e is the base of the Napierian logarithm and r the rate of the event in a giving time t[29].

Study perspective and guidelines followed

The study was conducted from the perspective of the Spanish National Health Care System (SNHCS), as a result of which only the direct health care costs are considered.

The general guidelines for the conduction of pharmacoeconomic analyses in Spain were followed[30], along with the guidelines published by the Canadian Coordinating Office for Health Technology Assessment[31] and the principles of good practice for decision analytic modeling in health-care evaluation of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[32].

Basic case premises

The basic case of the model contemplated the following summarized premises: 1) the patient cohort started treatment at 63 years of age, with a median follow up of 10 or 20 years; and 2) for the costs of the states and for the different complications mean values were used.

Cost estimation

The estimation of the costs of a disease treated with a given drug is based on identification and quantification of the health care resources involved and the designation of certain unit costs to those resources. Accordingly, the mean costs were estimated for a rep-

TABLE 2. **Design and results of the clinical trials: IES (Exemestane, EXE), ATAC (Anastrozole, ANA) and MA17 (Letrozole, LET)**

Item	EXE (IES 2004[6])		EXE (IES 2005[7])		ANA (ATAC 2002[8])		LET (MA17 2003[9])	
Total number of patients	4742		4742		6241		5187	
Years of prior treatment with TAM	2.4		2.4		–		5	
Daily doses (mg, oral route)								
EXE	25		25		–		–	
ANA	–		–		1		–	
LET	–		–		–		2.5	
TAM	20		20		20		–	
Median follow-up (months)	30.6		37.4		33.3		28.8	
Efficacy results	EXE	TAM	EXE	TAM	ANA	TAM	LET	PBO
Number of patients per group[a]	2362	2380	2362	2380	3125	3116	2593	2594
Number of events[b] (%)*	183 (7.7)	266 (11.2)	262 (11.1)	353 (14.8)	317 (10.1)	379 (12.1)	93 (3.6)	153 (5.6)
Recurrences and contralateral BC[c] (%)	144 (6.1)	227 (9.5)	205 (8.7)	290 (12.2)	239 (7.6)	298 (9.5)	75 (2.9)	132 (5.1)
Local recurrences	21	33	43	56	67	83	14	30
Distal recurrences	114	174	150	208	158	182	47	76
Contralateral BC	9	20	12	26	14	33	14	26
Deaths without recurrence	39	39	57	63	78	81	18	21
Total deaths (%)	93 (3.9)	106 (4.4)	152 (6.4)	187 (7.8)	200 (6.4)	203 (6.5)	31 (1.2)	42 (1.6)
Adverse events[d]	EXE	TAM	EXE	TAM	ANA	TAM	LET	PBO
Osteoporosis	171	134	175	145	–	–	124	97
Fractures (%)	72 (3.0)	53 (2.2)	NA	NA	183 (5.8)	115 (3.7)	77 (2.9)	63 (2.4)
Endometrial cancer	5	11	NA	NA	3	13	NA	NA
All secondary neoplasms (%)	27 (1.1)	53 (2.2)	NA	NA	104 (3.3)	106 (3.4)	NA	NA
VTE	30	55	41	69	64	109	NA	NA
DVT and/or PTE (%)	6 (0.2)	10 (0.4)	NA	NA	32 (1.0)	54 (1.7)	NA	NA
Myocardial infarction (%)	NA	NA	20 (0.8)	8 (0.3)	7.6 (2.4)	59 (1.9)	88 (3.4)	77 (2.9)
Stroke (%)	NA	NA	NA	NA	31 (1.0)	65 (2.1)	NA	NA
Cataracts	NA	NA	NA	NA	107	116	NA	NA
Reason of failure[e]								
Years from randomization	3		3		3		4	
Disease-free survival	0.68		0.73		0.83		0.57[f]	
(95%CI)	(0.56-0.82)		(0.62-0.86)		(0.71-0.96)		(0.43-0.75)	
p-value	< 0.001		0.0001		0.013		0.00008	
Overall survival	0.88		0.83		NA		0.76	
(95%CI)	(0.67-1.16)		(0.67-1.02)				(0.48-1.21)	
p-value	0.37		0.08				0.25	

ANA: anastrozole; ATAC: arimidex, tamoxifen alone or in combination; BC: breast cancer; EXE: exemestane; IES: intergroup exemestane study; LET: letrozole; NA: information not available in the article of the clinical trial; PBO: placebo; TAM: tamoxifen; PTE: pulmonary thromboembolism; VTE: venous thromboembolism (including less severe DVT, PTE and VTE); DVT: deep venous thrombosis.
Notes: [a]Randomized patients (analysis was made on an intent-to-treat (ITT) basis for both efficacy and toxicity); [b]Events contributing to disease-free survival: local recurrence in preserved breast, locoregional relapse, cancer in contralateral breast and deaths without recurrence. For example, in the IES study, after a median follow-up of 30.6 months, in the end-point there were 449 new events (183 in the EXE group and 266 in the TAM group). The disease-free survival analysis was performed according to the median follow-up times shown in the table; [c]Idem, excluding the deaths; [d]Economically relevant adverse events; [e]Hazard ratio or failure ratio (for recurrence and/or death), 95% confidence interval (95%CI) and statistical significance (P) of treatment with EXE or ANA in comparison with TAM, or with LET in comparison with PBO; [f]For local metastatic or contralateral recurrences corresponding to LET in comparison with PBO; *Indication is only made of the percentages for the main events and for those adverse events considered in the model to the effects of cost calculation.

resentative patient with OBC receiving therapy with EXE, ANA, LET, TAM or PBO. The costs of the health care resources used in the model are represented in euros (€) corresponding to the year 2004.

We only considered the annual costs of the patients in the aforementioned clinical trials from the moment of randomization onwards. The unit costs of the health care resources considered in the analysis are report-

TABLE 3. **Unit costs (€ corresponding to 2004) assigned to the resources and health states in the Markov model**

Resource (n.°, type)	Unit cost (€) (minimum-maximum)	Reference
Exemestane (EXE)		
Aromasil (30 tablets of 25 mg)[a]	170.02	11
Anastrozole (ANA)		
Arimidex (28 tablets of 1 mg)[a]	133.24	11
Letrozole (LET)		
Femara (30 tablets of 2.5 mg)[a]	170.02	11
Insegar (30 tablets of 2.5 mg)[a]	175.35	11
Tamoxifen (TAM)		
30 tablets of 10 mg[a]	4.43	11
500 tablets of 10 mg[a]	63.09	11
500 tablets of 20 mg[a]	102.36	11
Change of aromatase inhibitor		
Due to recurrence with EXE (annual)	1,919 (1,903-1,935)	c
Due to recurrence with ANA (annual)	2,161 (2,143-2,176)	c
Due to recurrence with LET (annual)	2,161 (2,143-2,176)	c
Complications		
Hip and pelvic fracture (DRG 236)	3,685 (2,284-5,555)	10
Endometrial cancer (PMC 2605)	4,323 (3,891-4,755)	10
DVT or PTE (DRG 128 and PMC 4125 and 4127)	3,909 (3,049-5,240)	10
Myocardial infarction (DRG 123 and PMC 301)	6,262 (5,581-7,105)	10
Stroke (DRG 16)	5,484 (2,700-12,748)	10
Second contralateral breast cancer[b]	5,623 (5,061-6,185)	10
Local recurrence of breast cancer[b]	6,346 (5,711-6,981)	10
Metastasis (PMC 204-209)	9,970 (7,802-12,320)	10

ANA: anastrozole; EXE: exemestane; DRG: diagnosis-related group; LET: letrozole; PMC: patient management categories; TAM: tamoxifen; PTE: pulmonary thromboembolism; DVT: deep venous thrombosis. [a]Customer selling price + 4% VAT; [b]Cost per process; [c]Estimation.

ed in table 3. The cost of the pharmacological treatments was estimated from the corresponding purchasing prices[11] and from the dosage instructions specified in the summary of product characteristics of the drugs used[33-36]. One hundred percent compliance was considered for all three treatment options compared.

The costs of the complications (fractures, second neoplasms, deep venous thrombosis, venous thromboembolism, myocardial infarction and stroke) were estimated from the corresponding diagnosis-related groups (DRGs) or the patient management categories (PMCs), and were obtained from a Spanish health care costs database[10] (table 3). The cost of OBC recurrence was deduced by estimating resources utilization and the microcosts in clinical practice during the disease process, based on two Spanish clinical practice guides[1,37]. The resources accounted in OBC were the following: visits to the Oncology Service, the Breast Unit, the Radiotherapy Service, and Primary Care Service; mammographs, biopsy (FNAB), chest X-rays, ultrasound and CT Scan, laboratory tests (full hematological study, liver and kidney functions, tumor antigens), bone gammagraphy, mastectomy; post-surgery admission to the Breast Unit, implantation of a reservoir, chemotherapy administration in the Day Care Hospital, standard treatment with TAC scheme (docetaxel, doxorubicin, cyclophosphamide at doses of 75/50/500 mg/m^2, administered in 6 cycles every 21 days) and, finally, radiotherapy for 6 weeks[1,37] (table 3).

Utilities estimation

Utilities were measured as quality adjusted life years (QALYs), where one QALY is one year of life multiplied by a weighting factor indicating patient quality of life during that year. This «weighting» factor can range from 0 (death or equivalent state) to 1 (perfect health). In the model the utilities were estimated for 63-year-old women with OBC at the start of the treatment, on the basis of those previously considered in the pharmacoeconomic studies published by Karnon et al[38] (BC), Gabriel et al[39] (fractures), Brunner et al[40] (thromboembolism) and Nicholson et al[41] (coronary disease). The utilities of the temporal states were estimated from the weighted means of the values corresponding to the transition states (table 4).

Sensitivity analysis

All estimations considered above constituted the basic case of the study. In order to assess the stability of the results and the consistency of the estimations, simple univariate sensitivity analyses were made of the basic case, considering the minimum or maxi-

TABLE 4. **Utilities (QALY) of the health states of the model in breast cancer. Patient age 63 years at the time of randomization**[38-41]

State	Utility
Disease-free without complications	0.820
Disease-free with complications	0.741
Local recurrence	0.718
Metastasis	0.462
Death	0.000

QALY: quality adjusted life year.

mum costs values, and the non-application of discounts.

RESULTS

Basic case

After 10 and 20 years of follow-up, more QALYs per patient would be gained with the EXE scheme after TAM (0.230-0.286 and 0.566-0.708, respectively) than with initial ANA (0.114 and 0.285) and LET after TAM (0.176 and 0.474) (table 5).
The cost of gaining one QALY (in 10 and 20 years) was lower with EXE scheme (50,801-62,522 € and 28,849-35,371 €, respectively) than with ANA (104,272 € and 62,477 €) and LET (91,210 € and 49,460 €) (table 5). The result proved to be stable for the cost per LYG (32,503-39,945 € and 15,568-19,139 € with EXE after 10 and 20 years; 65,313 € and 33,282 € with ANA; 57,128 € and 26,078 € with LET) (table 5).

Sensitivity analysis

The compared result of the three treatments was stable in the sensitivity analysis (table 6), with approximate costs per QALY gained that varied according to the scenario and with a follow-up of 10 and 20 years between 47,700-63,200 € and 25,200-35,700 €, respectively, with EXE; between 97,400 105,600 € and 50,500-62,500 €, respectively, with ANA; and between 85,500-92,300 € and 48,800-66,500 €, respectively, with LET.

DISCUSSION

According to the results of the model, the EXE scheme affords more QALYs and LYG than TAM or PBO, at a lesser cost than the ANA and LET schemes. As such, it is defined as the most cost-effective adjuvant therapy in the modeled population of post-

TABLE 5. **Results of the cost-utility analysis of adjuvant therapy with the aromatase inhibitors (exemestane, EXE; anastrozole, ANA; letrozole, LET) in comparison with tamoxifen (TAM) or placebo (PBO), in postmenopausal women with operable breast cancer and positive estrogen receptors**

Scenarios	EXE versus TAM IES 2004[6]	EXE versus TAM IES 2005[7]	ANA versus TAM[8]	LET versus PBO[9]
Time horizon: 10 years				
Cost with the aromatase inhibitor (€)	15,766	15,761	13,561	16,733
Cost with TAM (or PBO) (€)	1,237	1,381	1,674	680
Incremental cost (€)	14,529	14,380	11,887	16,053
QALY with the aromatase inhibitor	6.046	5.977	5.965	6.348
QALY with TAM (or PBO)	5.760	5.747	5.851	6.172
QALY gained	0.286	0.230	0.114	0.176
Cost per QALY gained (€)	*50,801*	*62,522*	*104,272*	*91,210*
LY with the aromatase inhibitor	8.567	8.454	8.465	9.042
LY with TAM (or PBO)	8.120	8.094	8.283	8.761
LYG	0.447	0.360	0.182	0.281
Cost per LYG (€)	*32,503*	*39,945*	*65,313*	*57,128*
Time horizon: 20 years				
Cost with the aromatase inhibitor (€)	22,183	21,990	18,944	24,540
Cost with TAM (or PBO) (€)	1,758	1,970	1,138	1,096
Incremental cost (€)	20,425	20,020	17,806	23,444
QALY with the aromatase inhibitor	8.480	8.303	8.274	9.279
QALY with TAM (or PBO)	7.772	7.737	7.989	8.805
QALY gained	0.708	0.566	0.285	0.474
Cost per QALY gained (€)	*28,849*	*35,371*	*62,477*	*49,460*
LY with the aromatase inhibitor	13.494	13.156	13.151	14.994
LY with TAM (or PBO)	12.182	12.110	12.616	14.095
LYG	1.312	1.046	0.535	0.899
Cost per LYG (€)	15,568	19,139	33,282	26,078

ANA: anastrozole; QALY: quality adjusted life year; LYG: life-year gained; EXE: exemestane; LET: letrozole; PBO: placebo; TAM: tamoxifen.

TABLE 6. **Results of the sensitivity analysis of the cost-utility model (cost per QALY gained) corresponding to the treatment of postmenopausal women with operable breast cancer and positive estrogen receptors with the aromatase inhibitors (exemestane, EXE; anastrozole, ANA; letrozole, LET) in comparison with tamoxifen (TAM) or placebo (PBO)**

Scenarios	EXE versus TAM IES 2004[6]	EXE versus TAM IES 2005[7]	ANA versus TAM[8]	LET versus PBO[9]
Time horizon: 10 years				
Basic case	50,801	62,522	104,272	91,210
Minimum costs	51,349	63,187	105,658	90,028
Maximum costs	50,273	62,026	103,254	92,363
Without discounts	47,717	58,483	97,461	85,484
Time horizon: 20 years				
Basic case	28,849	35,371	62,477	49,460
Minimum costs	29,148	35,733	58,645	48,827
Maximum costs	28,631	35,101	62,288	50,228
Without discounts	25,263	30,902	50,486	66,472

ANA: anastrozole; QALY: quality adjusted life year; LYG: life-year gained; EXE: exemestane; LET: letrozole; PBO: placebo; TAM: tamoxifen.

menopausal women with operable primary breast cancer and positive estrogen receptors.

In examining these results, it must be considered that this is a theoretical model (which by definition constitutes a simplified simulation of a true life situation) based on the findings of non-pragmatic clinical trials that do not directly compare treatments. Consequently, these results should be viewed as estimations for a representative patient and as such it may be useful as a tool for the taking of clinical decisions[12]. However, it must be taken into account that the model allowed the simulation of the costs and the consequences of treatment with a median follow-up of 10 and 20 years in women with OBC - this normally not being possible by means of clinical trials. Moreover, thanks to the Markov analysis, it was possible to perform a more «realistic» estimate of the course of the disease over 10 to 20 years than with a deterministic model[13]. Likewise, other «strengths» of the model should be pointed out: *1)* estimation of the unit costs and the use of resources was based on Spanish clinical practice guides[1,37]; and *2)* estimation of the transition probabilities was based on randomized clinical megatrials[6-9].

On the other hand, it should be taken into account that an indirect comparison of clinical trials was made that included similar patients and follow-up medians, though at the same time the schemes compared were very different: EXE after 2-3 years of monotherapy with TAM, ANA without prior treatment with TAM, and LET after 5 years of monotherapy with TAM. This latter comparison should have benefited the LET scheme in the analysis of effectiveness (because comparison was made with PBO) and penalized it in the cost analysis for this same reason (despite the low purchase cost of TAM). However, EXE yielded more QALYs and LYG, and the cost per patient was lower than with LET (table 5).

Another important aspect requiring mention is the difference in complications reported in the clinical trials. As an example, with ANA there were reports of stroke (though not with EXE and LET), and EXE and ANA reported secondary neoplasms and severe thromboembolism (though not with the LET scheme). It is to be presumed that these differences were real, though possibly some of these adverse effects went unreported due to protocol specifications of the clinical trials.

In an attempt to minimize the limitations of the model conservative premises were adopted in the basic case (as well as averaged values), and a sensitivity analysis was carried out considering several extreme scenarios.

In the same way as in another recently published pharmacoeconomic analysis comparing the efficiency of TAM alone, EXE after TAM and ANA alone[17], the present model confirmed that the cost per QALY gained or per LYG with the EXE scheme exceeded 30,000 € (regarded as the theoretically maximum acceptable amount for the reimbursement of a new treatment)[42], with a time horizon of 10 years and below 30,000 € per QALY gained or per LYG with a time horizon of 20 years. It must be pointed out, however, that according to two Spanish studies conducted in 1995 and 1998, hypolipidemic drugs, for example, are financed by the Spanish National Health Care System at a maximum cost per LYG of between 66,000 and the 240,000 €[43,44].

The results of this pharmacoeconomic analysis should be confirmed by means of pragmatic and randomized clinical trials directly comparing the efficacy, utilities, tolerance and use of health care resources of the therapeutic alternatives evaluated. In the meantime, and based on the results of the model, it can be concluded that compared to tamoxifen (or placebo, in the case of letrozole), exemestane would yield additional QALYs and LYG, at a lesser cost than

anastrozole and letrozole. As such, it can be defined as the most cost-effective therapy in the modeled population of postmenopausal women with operable breast cancer and positive estrogen receptors.

ACKNOWLEDGEMENTS

The authors thank César Picó (oncologist) for his inestimable contribution in the elaboration of this study during his professional collaboration in Pfizer España Medical Unit.

This study has been carried out with an unrestricted research grant from Pfizer, SA.

CONFLICTS OF INTEREST

Almudena del Castillo, Paloma González and Felisa Canorea are employees of Pfizer España. Juan Miguel Gil has no conflicts of interest with Pfizer España. Carlos Rubio-Terrés is employed by HERO Consulting, and has been responsible of the preparation of this manuscript.

References

1. OncoGuía de mama. Agencia de Evaluación de Tecnologías e Investigaciones Médicas. CatSalut. Departamento de Sanidad y Seguridad Social. Generalidad de Cataluña. Barcelona: noviembre 2003 (OG04/2003).
2. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet. 1896; 2:104-7.
3. Jensen EV, Jordan VC. The estrogen receptor: a model for molecular medicine. Clin Cancer Res. 2003;9:1980-9.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTG). Effects of chemotherapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365: 1687-717.
5. Ligibel JA, Winer EP. Clinical differences among the aromatase inhibitors. Clin Cancer Res. 2003;9:4735-95.
6. Coombes RC, Hall E, Gibson LJ, et al for the 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.
7. Coombes RC, Hall E, Snowdon CF, Bliss JM. A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen. Intergroup Exemestane Study. Updated survival analysis. 27th Annual San Antonio Breast Cancer Symposium. General Session 1. December 8, 2004. Available from: http://www.abstracts2view.com/sabcs/search.php?search = do&intMaxHits = 10&where%5B%5D = &andornot%5B%5D = &query = coombes (consulta: mayo de 2005).
8. The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002;359:2131-9.
9. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349:1793-802.
10. Gisbert R, Brosa M. Base de datos de costes sanitarios. Versión 1.5. Barcelona: Soikos, 2004.
11. Base de datos de medicamentos. Consejo General de Colegios Oficiales de Farmacéuticos. Disponible en URL: http://www.portalfarma.com/home.nsf (consulta: octubre, 2004).
12. Rubio-Terrés C, Sacristán JA, Badía X, Cobo E, García Alonso F, por el Grupo ECOMED. Métodos utilizados para realizar evaluaciones económicas de intervenciones sanitarias. Med Clin. 2004;122: 578-83.
13. Rubio Terrés C. Introducción a la utilización de los modelos de Markov en el análisis farmacoeconómico. Farm Hosp. 2000; 24:241-7.
14. DATA 3.5 for Healthcare. Williamstown (MA): TreeAge Software Inc, 1999.
15. Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer. 2004;101:1511-22.
16. Simons WR, Jones D, Buzdar A. Cost-effectiveness of anastrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer. Clin Ther. 2003;25:2972-87.
17. Skedgel C, Rayson D, Dewar R, Potvin K, Younis T. Economic evaluation of adjuvant hormonal options in postmenopausal women with breast cancer: Tamoxifen vs tamoxifen then exemestane vs anastrozole. 2005 ASCO Annual Meeting. Abstract 6040. Available from: http://www.asco.org/ac/1,1003,_12-002948-00_18-0038906,00.asp (consulta: mayo 2005).
18. Pérez EA, Mincey BA. Hormonal treatment of breast cancer in the extended adjuvant setting (mayo 2004). Available from: http://www.medscape.com/viewprogram/3082_pnt (consulta: mayo de 2005).
19. Lonning PE. Aromatase inhibitors in breast cancer. Endocrine-related Cancer. 2004;11:179-89.
20. Smith IE. Adjuvant hormonal therapy for breast cancer: results of the major trials. In: Smith IE, Thuerlimann B. Adjuvant Hormonal Therapy for Breast Cancer: An Evolving Process (Archived Web Conference) (enero 2005). Available from: http://www.medscape.com/viewprogram/3800_pnt (consulta: mayo de 2005).
21. Campos SM. Aromatase inhibitors for breast cancer in postmenopausal women. The Oncologist. 2004;9:126-36.
22. Gradishar WJ. Tamoxifen - What next? The Oncologist. 2004;9:378-84.
23. Annual Meetings of the American Society of Clinical Oncology. http://www.asco.org (consulta: mayo de 2005).
24. Annual San Antonio Breast Cancer Symposiums. http://www.sabcs.org (consulta: mayo de 2005).
25. Aromatase Inhibitors in the Adjuvant Setting: Updates on ATAC, MA-17, and IES. Fourth European Breast Cancer Conference March 16 - 20, 2004, Hamburg, Germany. Available from: http://www.medscape.com/viewarticle/474061? src = search (consulta: mayo de 2005).
26. Centro Nacional de Epidemiología. Mortalidad por causa, sexo y grupo de edad (CIE6). España, 1998. Disponible en URL: http://193.146.50.130. (consulta: mayo, 2005).
27. NICE. Guide to the methods of technology appraisal. London: National Institute for Clinical Excellence, April 2004.
28. INEbase. Tablas de mortalidad de la población de España 1998-1999. Datos nacionales. Disponible en URL: http://www.ine.es/inebase/cgi/axi (consulta: mayo, 2005).
29. Petitti DB. Meta-analysis, decision analysis and cost-effectiveness analysis. Methods for quantitative synthesis in medicine. New York: Oxford University Press; 1994.
30. Rovira J, Antoñanzas F. Economic analysis of health technologies and programmes. A Spanish proposal for methodological standardisation. Pharmacoeconomics. 1995;8:245-52.
31. Canadian Coordinating Office for Health Technology Assessment. Guideline for economic evaluation of pharmaceuticals: Canada. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), 1997.
32. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on good research practices-modeling studies. Value Health. 2003;6:9-17.
33. Ficha técnica: Aromasil (Exemestano). Pharmacia Spain, SA. Septiembre de 2004.
34. Ficha técnica: Arimidex (Anastrozol). AstraZeneca Farmacéutica Spain, SA. Julio de 2004.
35. Ficha técnica: Femara (Letrozol). Novartis Farmacéutica, SA. Febrero de 2005.
36. Ficha técnica: Nolvadex (Tamoxifeno). AstraZeneca Farmacéutica Spain, SA. Septiembre de 2003.
37. Albaina L, Viana C. Guías Clínicas de Atención Primaria: Cáncer de mama. Guías Clínicas 2003; 3 (7). Disponible en URL: http: //www.fisterra.com/guias2/mama. asp (consulta: abril de 2005).
38. Karnon J, Brown J, Adjuvant Breast Cancer (ABC) Steering Committee. Tamoxifen plus chemotherapy versus tamoxifen alone as adjuvant therapies for node-positive postmenopausal women

with early breast cancer: a stochastic economic evaluation. Pharmacoeconomics. 2002;20:119-37.
39. Gabriel SE, Kneeland TS, Melton LJ 3rd, Moncur MM, Ettinger B, Tosteson AN. Health-related quality of life in economic evaluations for osteoporosis: whose values should we use? Med Decis Making. 1999;19:141-8.
40. Brunner HI, Chan W-S, Ginsberg JS, Feldman BM. Longterm anticoagulation is preferable for patients with antiphospholipid antibody syndrome. Result of a decision analysis. Disponible en URL: http://www.jrheum.com/suscribers/02/03/tables/490-3.html (consulta: mayo de 2005).
41. Nicholson T, McGuire A, Milne R. Cost-utility of enoxaparin compared with unfractionated heparin in unstable coronary artery disease. BMC Cardiovasc Disord. 2001;1:2.
42. Sacristán JA, Oliva J, Del Llano J, Prieto L, Pinto JL. ¿Qué es una tecnología sanitaria eficiente en España? Gac Sanit. 2002; 16:334-43.
43. Plans Rubió P. Cost-effectiveness of pharmacologic treatments for the reduction of blood lipids. Med Clin (Barc). 1995;105: 327-33.
44. Plans-Rubió P. Cost-effectiveness of cardiovascular prevention programs in Spain. Int J Technol Assess Health Care. 1998; 14:320-30.