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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



PCT

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 **EXPEDIENTE No**

04-64979

54 **TITULO**

USO DEL ANASTROZOL PARA EL TRATAMIENTO DE MUJERES POSMENOPAUSICAS

QUE TIENEN CANCER PRECOZ DE MAMA

51 **CLASIFICACION INTERNACIONAL**

71 **SOLICITANTE**

ASTRAZENECA AB

DOMICILIO

SODERTALJE SUECIA

74 **APODERADO**

RAMIRO CASTRO DUQUE

22 **SANTAFE DE BOGOTA, D C**

CS

PETITORIO

AS: 94.200

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicación: 04064979 00000000 Folios: 50
Fecha (MD): 2004-07-06 17:17:07
Trámite: 011 PCT-PATENT 379 FASE NNCI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

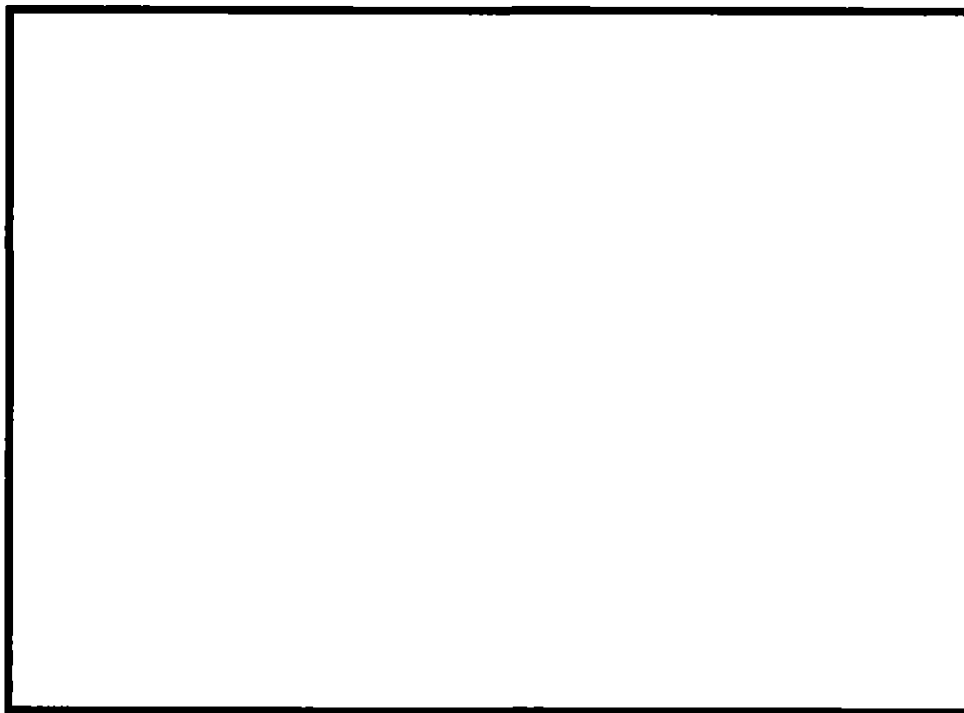
1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: ASTRAZENECA AB Dirección: S-151 85 Sodertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax E-mail		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 170.322 TP 1003
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5 PCT (86) Solicitud Internacional No. <u>PCT/GB02/05554</u> Fecha <u>06-12-2002</u> Publicación Internacional No. <u>WO 03/053438 A1</u> Fecha <u>03-07-2003</u>			
Título (54): <u>USO DEL ANASTROZOL PARA EL TRATAMIENTO DE MUJERES POSMENOPÁUSICAS QUE TIENEN CÁNCER PRECOZ DE MAMA</u>			
7 Clasificación Internacional (51) <u>A51K31/4196</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	GB	10-12-2001	0129457.8
9 Comprobante de pago No. <u>04-39.541</u> Fecha <u>06-07-2004</u>			
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arie final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☒ Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA.



12 Solicito la concesión de la patente

NOMBRE. RAMIRO CASTRO DUCUE

FIRMA.

C.C. 170322 de Bogotá F.P 1003 del C.S.J

Instrucciones para la presentación de los anexos ver reverso de esta página

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SUPERINDUSTRIA Y COMERCIO
Radicación : 04064979 00000000 Folios: 50
Fecha (RMD): 2004-07-08 17:17:07
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 39,541
FECHA : MAYO 17 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21740989	17/05/2004	22,697,000.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

800: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

h4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
3 July 2003 (03.07.2003)

PCT

(10) International Publication Number
WO 03/053438 A1(51) International Patent Classification: A61K 31/4196,
A61P 35/00(74) Agent: ASTRAZENECA; Global Intellectual Property,
Maraiside, Alderley Park, Macclesfield, Cheshire SK10
4TG (GB).

(21) International Application Number: PCT/GB02/05554

(22) International Filing Date: 6 December 2002 (06.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0129457.8 10 December 2001 (10.12.2001) GB(71) Applicant (for all designated States except MG, US): AS-
TRAZENECA AB [SE/SE]; Sodertalje, S-151 85 (SE).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GR, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Borserim patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).(71) Applicant (for MG only): ASTRAZENECA UK LIM-
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clesfield, Cheshire SK10 4TG (GB). DUKES, Michael
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4TG (GB).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 03/053438 A1

(54) Title: USE OF ANASTROZOLE FOR THE TREATMENT OF POST-MENOPAUSAL WOMEN HAVING EARLY BREAST
CANCER(57) Abstract: The invention provides the use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of
a medicament for the reduction of the rate of recurrence of cancer in a woman having early breast cancer. The invention further
provides the use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction
of the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer.

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USE OF ANASTROZOLE FOR THE TREATMENT OF POST-MENOPAUSAL WOMEN HAVING EARLY BREAST CANCER

In post-menopausal women, the anti-oestrogen tamoxifen citrate (NOLVADEX[™]) has become accepted as standard first-line treatment of advanced breast cancer. Furthermore, over 34,000 women have taken part in clinical trials of adjuvant tamoxifen following primary surgery. The anti-cancer effect of tamoxifen citrate (hereinafter "tamoxifen") is related to its ability to compete with oestrogen for binding sites in target tissue such as the breast. In addition, it has a variety of other complicated mechanisms which may mediate its effect, including the induction of transforming growth factor beta from stromal fibroblasts, the reduction in circulating levels of insulin-like growth factor 1, the inhibition of angiogenesis and the induction of apoptosis. Nevertheless, the oestrogen receptor (ER) status of the tumour still remains a powerful predictor of response.

In advanced disease, approximately 70% of patients who are ER and progesterone receptor (PR) positive will respond to tamoxifen, compared with <10% of patients who are ER and PR negative (Muss, 1992 Breast Cancer Research and Treatment 21: 51-26). In the adjuvant setting, the ER status of the primary tumour is less discriminatory and the latest overview of the Early Breast Cancer Trialists' Co-operative Group (EBCTCG) [Lancet 351: 1451-1467] has suggested that only pre-menopausal ER negative patients are unlikely to benefit from adjuvant tamoxifen. It is likely that other endocrine approaches to the adjuvant treatment of early breast cancer, which involve reducing the level of circulating oestradiol (ovarian suppression and aromatase inhibition), are dependant on an intact oestrogen receptor mechanism at the sites of metastatic disease.

Aromatase inhibitors are a class of compounds that act systematically to inhibit oestrogen synthesis in tissues. These compounds prevent oestrogen biosynthesis by inhibiting the enzyme aromatase, which catalyses the conversion of adrenal androgens (androstenedione and testosterone) to oestrogens (oestrogen and oestradiol). There has therefore been interest in developing these compounds as potential therapies for hormone responsive breast cancer in post-menopausal women.

Aminoglutethimide was the first aromatase inhibitor to be approved for treatment of breast cancer and has proven efficacy in post-menopausal women with advanced breast cancer (Stuart-Harris et al 1984, Acta Oncology 27: 721-728). Wider use of the drug has been limited by its lack of specificity, resulting in a requirement for concomitant administration of corticosteroids, and the occurrence of troublesome side effects (Wells et al

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1978, *Annals Surgery* 187: 475-487). Consequently, research has been focused on the development of aromatase inhibitors with greater specificity and a better tolerability profile.

ARIMIDEX™ (anastrozole) is a non-steroidal aromatase inhibitor which is highly selective, well tolerated and is effective in treating advanced breast cancer (Buzdar et al 1995, *The Breast* 4(3): 256-257 Abs 104; Jonat et al 1995, *European Journal of Cancer* 32A(3): 404-412; Plourde et al 1995, *Journal of Steroid Biochemistry* 53:175-179). (Further information on the clinical experience with Arimidex can be found in the prescribing information sheet for Arimidex). Anastrozole is described in U.S. patent RE 366717, which is incorporated by reference herein.

10 The use of adjuvant systemic therapies following local treatment of breast cancer (surgery with or without radiotherapy) has resulted in an increase in disease-free survival and overall survival (EBCTCG, 1992, *Lancet* 339: 1-15, 71-85). Tamoxifen is currently the agent of choice as adjuvant endocrine therapy for breast cancer. Patients treated with adjuvant tamoxifen for two years or more can expect an annual reduction in recurrence of 39% and an
15 annual reduction in mortality of 24%, in the absence of concomitant chemotherapy (EBCTCG, 1992). In pre-menopausal women with oestrogen receptor positive tumours, the benefit is as great as for post-menopausal women, but there seems little benefit for ER negative pre-menopausal women. In contrast, both ER positive and ER negative post-menopausal women will benefit, although there is a suggestion that the greater the ER level in
20 the primary tumour the greater the likelihood of benefit.

Tamoxifen therapy also provides other beneficial effects, which relate to the partial agonistic action of the drug. These include cholesterol-lowering effects (Love et al 1994, *Journal of the National Cancer Institute* 86: 1534-1539), cardio-protective effects (McDonald et al 1995, *British Medical Journal* 311: 977-980) and protection against bone loss (Love et al
25 1992, *New England Journal of Medicine* 326: 852-856). However, adverse events are also associated with tamoxifen which can be classified as being either consequences of the anti-oestrogenic action of the drug, e.g. hot flushes, vaginal bleeding or discharge or dryness, or more general effects, e.g. gastro-intestinal intolerance, tumour flare, light headedness, skin rash.

30 An increased incidence of endometrial cancer has also been reported in association with tamoxifen treatment. The incidence and pattern of this increase suggest that the underlying mechanism may be related to the oestrogenic properties of tamoxifen. Uterine

fibroids and other endometrial changes including hyperplasia and polyps have also been reported in patients receiving tamoxifen.

Notwithstanding the good results obtained with tamoxifen as an adjuvant therapy in patients with early breast cancer, there is a good rationale to evaluate alternative endocrine modalities in this patient population alone although it could be predicted that combinations therapies could be more effective. Benefits could include a longer duration of effectiveness and possible freedom from the side effects associated with the partial agonist properties of tamoxifen.

One possible combination is a combination of anastrozole and tamoxifen in the light of the proven efficacy of anastrozole in advanced breast cancer, its favourable tolerability and a mechanism of action distinct from tamoxifen.

An early trial, using the aromatase inhibitor aminoglutethimide alone, demonstrated improvements in relapse-free survival and overall survival, when compared to placebo (Coombes et al, 1987, Cancer Research 47, 2494-2497), but the supportive management required, and the restricted patient acceptability prevented further development. In contrast, anastrozole, in phase III trials for the second line treatment of advanced breast cancer, not only demonstrated similar efficacy to megestrol acetate, but also a favourable tolerability profile, especially with respect to weight gain.

NOLVADEX™ and ARIMIDEX™ are trademarks and are the property of the AstraZeneca group of companies.

Surprisingly we have found that anastrozole is efficacious and well tolerated in the adjuvant treatment of breast cancer, but even more surprisingly we have found that anastrozole is significantly more effective than tamoxifen for disease-free survival in early breast cancer. Thus according to a first aspect of the invention there is provided herein a method of reducing the rate of recurrence of cancer in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole, or its pharmaceutically acceptable salt, to said woman.

According to a further feature of the first aspect of the invention there is provided the use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction of the rate of recurrence of cancer in a post-menopausal woman having early breast cancer.

In women who are receiving adjuvant treatment for breast cancer, the cancer can re-emerge in the same breast as the original cancer or may occur in the other breast, referred

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to as contralateral breast cancer. Surprisingly we have also found that anastrozole was significantly more effective than tamoxifen in terms of incidence of contralateral breast cancer, thus according to a second aspect of the invention there is provided herein a method of reducing the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole, or its pharmaceutically acceptable salt, to a said woman.

According to a further feature of the second aspect of the invention there is provided the use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction of the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer.

Tamoxifen has been approved for use for adjuvant therapy for early breast cancer and thus it could be expected that anastrozole would be synergistic with tamoxifen, depleting the oestrogen receptor of its natural ligand, whilst allowing tamoxifen to exert its beneficial effect via alternative biological mechanisms. However, surprisingly, we have found that rather than being more effective than tamoxifen alone, a combination of anastrozole and tamoxifen was only equivalent to tamoxifen and significantly worse than anastrozole alone for adjuvant treatment of early breast cancer. Thus, surprisingly tamoxifen reduces the efficacy of anastrozole for the adjuvant treatment of early breast cancer. Thus, according to a third aspect of the invention there is provided a method of reducing the rate of recurrence of cancer in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole or its pharmaceutically acceptable salt to said woman wherein the anastrozole or its pharmaceutically acceptable salt is administered in the substantial absence of tamoxifen.

According to a further feature of the third aspect of the invention there is provided the use of anastrozole or a pharmaceutically acceptable salt thereof, substantially in the absence of tamoxifen in the preparation of a medicament for the reduction of the rate of recurrence of cancer in a post-menopausal woman having early breast cancer.

The phrase 'substantially in the absence of tamoxifen' means that the anastrozole is administered to the patient in the absence of tamoxifen. Patients receiving adjuvant therapy for early breast cancer are likely to have previously received tamoxifen treatment. Thus, this phrase relates to the anastrozole medication rather than the patient being treated.

Surprisingly we have also found that the combination of anastrozole and tamoxifen was only equivalent to tamoxifen and significantly worse than anastrozole alone in the

prevention of contralateral breast cancer. Thus, according to a fourth aspect of the invention there is provided a method of reducing the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole or its pharmaceutically acceptable salt to said woman wherein the
5 anastrozole or its pharmaceutically acceptable salt is administered in the substantial absence of tamoxifen.

According to a further feature of the fourth aspect of the invention there is provided the use of anastrozole or a pharmaceutically acceptable salt thereof substantially in the absence of tamoxifen in the preparation of a medicament for the reduction of the rate of a new
10 contralateral primary tumour in a post-menopausal woman having early breast cancer.

In each aspect of the invention the anastrozole, or its pharmaceutically acceptable salt is preferably administered as an adjuvant to surgery, chemotherapy or radiation. Surgery includes lumpectomy, quadrantectomy or mastectomy.

In another aspect of the invention, the anastrozole or its pharmaceutically acceptable
15 salt is administered to a woman having early breast cancer and the woman is oestrogen receptor positive or progesterone receptor positive, more preferably oestrogen receptor positive, most preferably oestrogen receptor positive and progesterone receptor positive.

Anastrozole can be administered at a dose between 0.1 and 10 mg/day, preferably, between 0.5 and 5mg/day, most preferably anastrozole is administered at 1mg/day.

As described above in one aspect of the invention the anastrozole, or its
20 pharmaceutically acceptable salt, is administered in the substantial absence of tamoxifen. However, in a further feature of the third and fourth aspect of the invention the anastrozole is administered in the substantial absence of an anti-oestrogen agent such as arzoxifene, tamoxifen, fulvestrant, lasofoxifene, raloxifene, toremifene, trilostane or TSE 424,
25 preferably in the absence of tamoxifen.

Treatment of post-menopausal women is preferred as described above, however, treatment of pre-menopausal women is also contemplated.

In one aspect of the invention, the administration is carried continuously, for a least one year, preferably for at least two years. Five years continuous treatment is most preferred,
30 although greater than five years treatment is also contemplated.

In carrying out the methods of the present invention, anastrozole may be provided in various formulations such as parentally (e.g. aqueous or oily suspensions) or orally (e.g., tablets, powders, capsules, granules, aqueous or oily suspensions). Preferably, anastrozole is

provided in orally available formulations preferably in formulations having from 1 to 10mg anastrozole, most preferably 1mg. In the study described below, 1mg tablets were used.

The invention will now be illustrated with reference to the following non-limiting example and the following figures and tables. In this figure legends HR is an abbreviation of hazard ratio. Values wherein the hazard ratio is less than 1.00 mean the values are in favour of anastrozole or the combination of anastrozole and tamoxifen as appropriate. Values wherein the hazard ratio is greater than 1.00 means that the values are in favour of tamoxifen. The 'time to events' is the time between the commencement of receiving therapy within the trial and diagnosis of recurrence of breast cancer. Figures 1-3 depict Kaplan-Meier Curves which would be familiar to the skilled man, however, more information can be found in Modelling Survival Data in Medical Research by D.Collett (Published by Chapman & Hall, 1994).

Figure 1 - Kaplan-Meier Curves of disease-free survival in ITT population

The Figure shows 'Time to events (months)' on the X axis and 'Proportion of patients event free (%)' on the Y axis.

	HR	95.2% CI	p-value
anastrozole vs tamoxifen	0.83	0.71-0.96	0.0129
combination vs tamoxifen	1.02	0.88-1.18	0.7718

This figure shows that in the overall population, anastrozole is superior to tamoxifen with a significant reduction in the rate of disease recurrence, the combination is similar to that of tamoxifen for the overall population.

Figure 2 - Kaplan-Meier Curves of disease-free survival in receptor positive population

The Figure shows 'Time to events (months)' on the X axis and 'Proportion of patients event free (%)' on the Y axis.

	HR	95.2% CI	P-value
anastrozole vs tamoxifen	0.78	0.65-0.93	0.0054
combination vs tamoxifen	1.02	0.87-1.21	0.7786

This figures shows that in the overall population, anastrozole is superior to tamoxifen with a significant reduction in the rate of disease recurrence, the combination is similar to that of tamoxifen for the overall population.

Figure 3 - Analysis of the incidence of new (contralateral) breast primaries;

The figure shows 'Time to first contralateral new primary (months)' on the X axis and 'Proportion without contralateral breast cancer (%)' on the Y axis.

	HR	95.2% CI	P-value
anastrozole vs tamoxifen	0.42	0.22-0.79	0.0068
combination vs tamoxifen	0.84	0.51-1.40	0.5132

This figures shows the superiority of anastrozole is also evident in terms of the incidence of new primary (contralateral) breast cancer, relative to tamoxifen, whereas the combination is similar to tamoxifen.

Figure 4 – Significant differences in pre-defined adverse events between anastrozole and tamoxifen expressed as a percent. Adverse events less prevalent in anastrozole are shown on the left hand side of the figure and adverse events less prevalent with tamoxifen are shown on the right of the figure. The adverse events shown are as follows:

- (i) hot flushes
- (ii) Musculoskeletal Disorders
- (iii) Weight gain (proportion with ≥10% gain in body weight from baseline in year 2)
- (iv) Fractures of any bone
- (v) Fractures of hip, spine , wrist (these fractures are indicators of osteoporosis)
- (vi) Vaginal bleeding
- (vii) Vaginal discharge
- (viii) Endometrial Cancer
- (ix) Ischaemic Cardiovascular Accidents
- (x) Venous Thromboembolic Events
- (xi) Deep Vein Thrombosis

This figure shows that Anastrozole is well tolerated and no unexpected safety concerns emerged in the adjuvant programme.

Table 1 - Summary of the characteristics of the patients in the trial;

Table 2 – Summary of the disease characteristics of the patients in the trial; and

Table 3 – First events in ITT population.

Abbreviations: CI – confidence interval;
HR – hazard ratio;
ITT – intention to treat;
od – once daily; and

OR – odds ratio.

A trial was designed and conducted to compare the efficacy and safety of tamoxifen and anastrozole alone and with anastrozole and tamoxifen in combination as adjuvant treatment for post-menopausal women with early breast cancer, who have completed their
5 primary therapy. The trial was designed to compare tamoxifen (20mg once daily [od]) and anastrozole (1mg od) and to compare tamoxifen (20mg od) and the combination of anastrozole (1mg od) plus tamoxifen (20mg od) as adjuvant treatment in terms of:

- a) time to recurrence of breast cancer (defined as the earliest of local or distant recurrence, new primary breast cancer, or death); and
 - 10 b) safety and side effects.
- Secondary objectives of this trial were to compare (i) tamoxifen and anastrozole and (ii) to compare tamoxifen and the combination of anastrozole plus tamoxifen as adjuvant treatment in terms of:
- a) time to distant recurrence;
 - 15 b) survival; and
 - c) incidence of new breast primaries.

Specifically, the trial was designed as a randomised, double-blind, multicentre trial to compare the efficacy and safety of tamoxifen alone, anastrozole alone and anastrozole in combination with tamoxifen as adjuvant treatment for breast cancer in post-menopausal
20 women. Patients who meet the eligibility criteria were randomised on a 1:1:1 basis into one of three oral treatment schedules to receive one of the following:

- a. active anastrozole 1mg once daily plus tamoxifen placebo once daily;
- b. active tamoxifen 20mg once daily plus anastrozole placebo once daily;
- c. active anastrozole 1mg once daily in combination with active tamoxifen 20mg once daily.

25 Patients were assessed at entry, 3 months, 6 months and thereafter at 6-month intervals. Patients were recruited from 381 centres and in 21 countries. The patients were recruited between July 1996 and March 2000. Nine thousand three hundred and sixty-six (9366) patients entered the trial and were given the drugs as follows: 1) Anastrozole (n=3125), 2) tamoxifen (n=2116) and 3) combination (n=3125).

30 In order to be eligible for entry into the trial the patients had to satisfy all the following:

- a) patients with histologically proven operable invasive breast cancer;

b) patients who have completed all primary surgery and chemotherapy (if given), and are candidates to receive hormonal adjuvant therapy; and

c) women defined as post-menopausal according to one or more of the following:-

(i) aged 60 or more

5 (ii) aged 45-59 years and satisfying one or more of the following criteria:

- amenorrhoea for at least 12 months and intact uterus;

- amenorrhoea for less than 12 months and FSH within the post-menopausal range; including:

- patients who have had a hysterectomy;

10 - patients who have received HRT;

- patients rendered amenorrhoeic by adjuvant chemotherapy (such patients must have FSH measured at least 6 weeks after stopping chemotherapy);

- bilateral oophorectomy.

Patients with any of the following were excluded from the trial:

15 a) patients in whom there was any clinical evidence of metastatic disease;

b) patients who, for whatever reason (e.g. confusion, infirmity, alcoholism), were unlikely to comply with trial requirements;

c) patients whose chemotherapy was started more than 8 weeks (i.e., 56 days) after completion of primary surgery or whose chemotherapy was completed more than 8 weeks (i.e., 56 days) before starting randomised treatment; Chemotherapy if given should be given post-operatively i.e. patients who receive neoadjuvant chemotherapy were ineligible;

20 d) patients who had not received chemotherapy and whose primary surgery was completed more than 8 weeks (i.e., 56 days) before starting randomised treatment;

e) patients who have received previous hormonal therapy as adjuvant treatment for breast cancer, unless:-

25 (i) this was tamoxifen started prior to first surgical procedure and received for less than 29 days; or

(ii) this was hormonal therapy received pre-surgery in the context of a formal trial,

approved by the Steering Committee;

30 f) patients who have received tamoxifen as part of any breast cancer prevention trials,;

g) patients unwilling to stop taking any drug known to affect sex hormonal status (including HRT), or in whom it would be inappropriate to stop;

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- h) previous history of invasive breast cancer at any time or other invasive malignancy within the last 10 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied;
- i) any severe concomitant disease which would place the patient at unusual risk or confound the results of the trial, e.g. strong family history of osteoporosis, severe renal or hepatic impairment (defined as AST or ALT greater than three times the upper limit of the reference range); or
- j) treatment with non-approved or experimental drug during the 3 months before randomisation;
- 10 k) patients considered by the investigator to be at risk of transiting any infection through blood or other body fluids.

The double blind trial used both active and placebo anastrozole and tamoxifen tablets, in order to maintain blindness to trial therapy. Anastrozole 1 mg and matching anastrozole placebo were supplied as white, film-coated tablets. Tamoxifen 20mg active tablets and matching tamoxifen placebo were supplied as white, round, biconvex tablets. Patients were randomised to receive one of three oral therapy regimens. The daily dose is one tablet of anastrozole (1mg active or placebo) plus one tablet of tamoxifen (20mg active or placebo). Patients were instructed to take their daily dose at approximately the same time each day. At entry to the trial patients received either a 13-week supply or a 26-week supply of trial material. Patients who received a 13-week supply received a further 13-week supply at the first follow-up visit (3-months). From the 6-month visit onwards, patients received a 26-week supply. In order to assess compliance, patients were asked to return all unused tablets at each visit.

Therapy was started as soon as possible after randomisation, but not more than 8 weeks after completion of surgery and chemotherapy. Patients who have received primary chemotherapy may have started randomised treatment up to a maximum of 8 weeks after completion of chemotherapy or sooner in patients whose blood counts was returning or had returned to normal. Primary chemotherapy must have started within 8 weeks of completing primary surgery. Patients who stop primary chemotherapy before completion of the planned number of cycles may also be randomised. With the exception of the trial therapy, drugs which affect sex hormone status or prevent recurrence of disease were prohibited from use after randomisation until confirmation of disease recurrence. These drugs include the following:-

- cytotoxic chemotherapy;
oral administration of ketoconazole (antifungal) or related compounds (i.e. topical applications are acceptable);
other hormonal treatments for breast cancer.
- 5 A procedure provided that if patients suffer serious menopausal symptoms, e.g., vaginal dryness or bleeding, hot flushes, abdominal cramps, dyspareunia, the following action should be taken:-
- a. report the symptom as an adverse event;
b. if patients were willing, carry on with randomised treatment;
- 10 c. if necessary, patients may have taken progestins for 3-6 months.
- If up to 6 months treatment with progestins failed to control menopausal symptoms, HRT and/or oestrogen creams may be prescribed, and randomised treatment may continue.
- The following information was obtained and evaluated from the patient:
- a) Date of birth and ethnic origin (recorded at entry);
- 15 b) Any relevant past medical history, any concurrent illness, whether or not the patient has had a hysterectomy, previously smoked or had previous HRT (recorded at entry);
- c) All concomitant medication/treatment (recorded at entry);
- d) Height (measured at entry) and weight (measured at entry and until patient stops randomised treatment);
- 20 e) Breast cancer history-Surgical procedure, date of surgery, size and grade of primary tumour, nodal status, ER and PR status (where known), and details of any radiotherapy, chemotherapy and pre-surgical tamoxifen received (recorded at entry);
- f) The following routine laboratory assessments was performed at entry: haemoglobin, platelet count, leucocytes, creatinine, total bilirubin, alkaline phosphatase, either aspartate aminotransferase or alanine aminotransferase, sodium, potassium and urea. If clinically
- 25 indicated, further laboratory assessments were made until the patient stops the randomised treatment. Any clinically significant abnormal values should have been recorded as adverse events, unless resulting from disease recurrence. Blood samples were evaluated locally and the laboratory print-outs held in the patient's clinic/hospital records.
- 30 Patients were reviewed for recurrence of breast cancer at all follow-up visits, using the following criteria, which are based on British Breast Group recommendations:-

<i><u>SITE OF RECURRENCE</u></i>	<i><u>METHOD OF CONFIRMATION</u></i>
<u>LOCO-REGIONAL</u>	
1. Ipsilateral breast (including DCIS) *	Histology or cytology
2. Chest wall	Histology or cytology
3. Axillary lymph nodes	Histology or cytology
4. Other regional nodes (i.e. supraclavicular and internal mammary)	Histology or cytology
<u>DISTANT</u>	
5. Skeletal	CT * scan, or bone scan with x-ray evaluation of hot spots. Biopsy may be necessary in the case of a single lesion.
6. Pulmonary	Chest x-ray
7. Hepatic	CT or US * scan
8. Other distant	Imaging and/or biopsy. (Rising tumour markers alone, eg CA 15.3, are unacceptable)

Ductal Carcinoma In Situ

★ Computed Tomography

Ultra-sound

5 New breast primaries (either contralateral or ipsilateral) were regarded as disease recurrence events in the statistical analyses of time to recurrence.

The primary statistical endpoint of the trial was time to disease recurrence (locoregional or distant recurrence, new primary breast cancer or death from any cause) and safety/tolerability. The secondary statistical endpoints were time to distant recurrence, time to death, the incidence of new breast primaries and the incidence of pre-defined adverse events. In summary, two treatment comparisons were made: (1) anastrozole alone compared to tamoxifen alone and (2) tamoxifen alone compared to anastrozole and tamoxifen in combination.

For time to disease recurrence, time to distant recurrence and time to death, the primary analysis strategy, included all randomised patients and was performed according to randomised treatment (i.e. 'intention to treat'), with two equally important components:

- (i) The log-rank test was used to provide a basic comparison of treatment groups without
5 adjusting for potential prognostic factors. (This is equivalent to fitting the Cox proportional hazards model without adjusting for baseline covariates). 1056 events were required for statistical power.
- (ii) The Cox proportional hazards model was fitted, adjusting for baseline receptor status, nodal status, primary tumour size, previous chemotherapy, age and race. A global test of
10 interactions, included all 2 way interactions of each of these prognostic factors with randomised treatment, was undertaken at the 1% level in order to assess whether the treatment comparisons are consistent across different values of the factors. The assumption of proportional hazards was also checked for each prognostic factor using time
15 dependent variables. If there was a departure in the assumption (at the 5% level) then the factor should be included as a stratified variable.

The incidence rates of contralateral breast cancer was formally compared between randomised treatment groups. The primary analysis was based on an intention to treat approach.

A secondary 'per protocol' analysis and a subgroup analysis in patients with oestrogen
20 receptor (ER) positive and/or progesterone receptor (PR) positive tumours, patients with ER negative and PR negative tumours, and all other patients, was also undertaken.

At the major analysis, the incidence rates of the following pre-defined adverse events was formally compared between treatment groups defined by treatment received: hot flushes, nausea and vomiting, asthenia, mood disturbances, musculo-skeletal disorders, vaginal
25 bleeding, vaginal discharge, endometrial cancer, fractures, cataract, venous thromboembolic events, and ischaemic cardiovascular disease. The primary analysis includes all patients who received trial treatment, analysed according to treatment received. A secondary subgroup analysis was also be undertaken, analysed according to trial treatment received, in patients with oestrogen receptor (ER) positive and/or progesterone receptor (PR) positive tumours,
30 patients with ER negative and PR negative tumours, and all other patients remaining safety data was summarised and presented by treatment received. A summary of the methodology is set forth in Figure 3.



Definitions for the statistical analysis:

Time to event (disease recurrence, distant disease recurrence, death) was measured from the date of randomisation. Patients who have not experienced the event at the time of analysis were right-censored at the most recent date of assessment.

- 5 Disease recurrence was the earliest of local or distant recurrence new primary breast cancer (contralateral or ipsilateral) or death.

Distant disease recurrence was the earliest of distant recurrence or death.

- Disease Stage I at entry was defined as a primary tumour of 2cm or less in its largest dimension and no evidence of lymph node involvement (i.e. the number of positive nodes is zero or axillary surgery was not clinically indicated and therefore was not undertaken). If a patient did satisfy the above criteria, they were considered to be Disease Stage II.

- Results of the study are set forth in Figures 1, 2, 3 and 4 and Table 1, 2 and 3. The results relate to a trial consisting of 9,366 patients with a median duration of therapy of 30.7 months with a median follow up of 34.3 months. The total number of first events recorded, i.e. re-emergence of breast cancer, was 1079 of which 766 were in the receptor positive population. The results show that anastrozole is superior to tamoxifen in terms of disease-free survival in the overall population (HR = 0.83) and in the receptor-positive patients (HR = 0.78).

- Accordingly, the results of the main analysis of the trial indicate a 17% reduction in the rate of recurrence events (which includes locoregional, distant, and contralateral events, as well as deaths) for the patients receiving anastrozole vs. those receiving tamoxifen. Within the hormone receptor positive (oestrogen receptor positive and/or progesterone receptor positive) patients, there was a 22% reduction in recurrence rate for anastrozole vs. tamoxifen patients.

- 25 The results also show that anastrozole is superior to tamoxifen in terms of the incidence of contralateral breast cancer in the overall population (OR = 0.42). For the incidence of new (contralateral) breast primary tumours the odds were 0.42 for anastrozole when compared to tamoxifen (a value of 1.00 would show equivalence) in the overall population.

- 30 Anastrozole was significantly better tolerated (vs. tamoxifen) with respect to endometrial cancer, vaginal bleeding, vaginal discharge, ischemic cerebrovascular events, venous thromboembolic events, hot flushes and weight gain. Tamoxifen was better tolerated with respect to musculoskeletal disorders and fractures.

Table 1- Patient Characteristics

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)
Mean age (years)	64.1	64.1	64.3
Mean weight (kg)	70.8	71.1	71.3
Receptor status (%)			
Positive	83.7	83.3	84.0
Negative	7.4	8.0	6.9
Other	8.9	8.7	9.1
Primary treatment (%)			
Mastectomy	47.8	47.3	48.1
Axillary surgery	95.5	95.7	95.2
Radiotherapy	63.3	62.5	62.0
Chemotherapy	22.3	20.8	20.8
Prior tamoxifen	1.6	1.7	1.7

R
K**Table 2- Disease Characteristics**

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)
Primary tumour size (%)			
T1 (≤ 2cm)	63.9	62.9	64.1
T2 (> 2cm and ≤ 5cm)	32.6	34.2	32.9
T3 (> 5cm)	2.7	2.2	2.3
Nodal status (%)			
Node +ve	34.9	33.6	33.5
Grading (%)			
Well differentiated	20.8	20.5	21.2
Moderately differentiated	46.8	47.8	46.6
Poorly/undifferentiated	23.7	23.3	23.7
Not assessed/recorded	8.7	8.4	8.5

Table 3 – First events in ITT population

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)
First event	317	379	383
Locoregional	67	83	81
Distant	156	181	202
Contralateral (invasive)	9	30	23
Contralateral (DCIS)	5	3	5
Death — breast cancer	2	1	2
Death — other reason	78	81	70

13
X

- 18 -

Claims

1. The use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction of the rate of recurrence of cancer in a post-menopausal woman having early breast cancer.
2. The use of anastrozole, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the reduction of the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer.
3. The use according to Claim 1 or Claim 2 wherein the anastrozole is provided substantially in the absence of an anti-oestrogen agent.
4. The use according to Claim 3 wherein the anti-oestrogen agent is tamoxifen.
5. The use according to any one of the preceding claims wherein the woman having said early breast cancer is oestrogen receptor positive or progesterone receptor positive.
6. The use according to Claim 5 wherein the woman having said early breast cancer is oestrogen receptor positive and progesterone receptor positive.
7. The use according to any one of the preceding claims wherein the anastrozole is provided for administration at a dose of 1mg/per day.
8. A method of reducing the rate of recurrence of cancer in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole, or its pharmaceutically acceptable salt, to said woman.
9. A method of reducing the rate of a new contralateral primary tumour in a post-menopausal woman having early breast cancer comprising administering an effective amount of anastrozole, or its pharmaceutically acceptable salt, to a said woman.

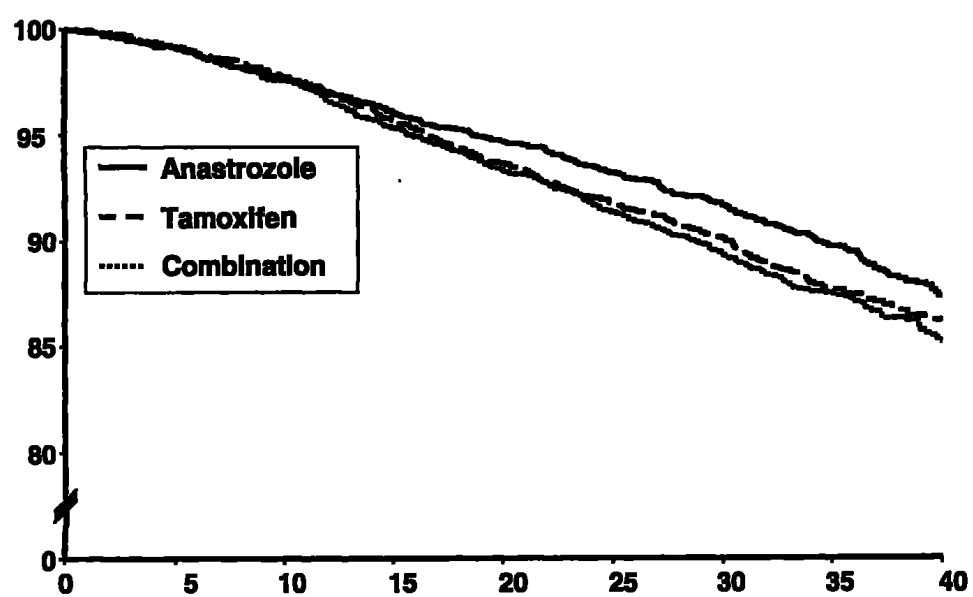


Figure 1

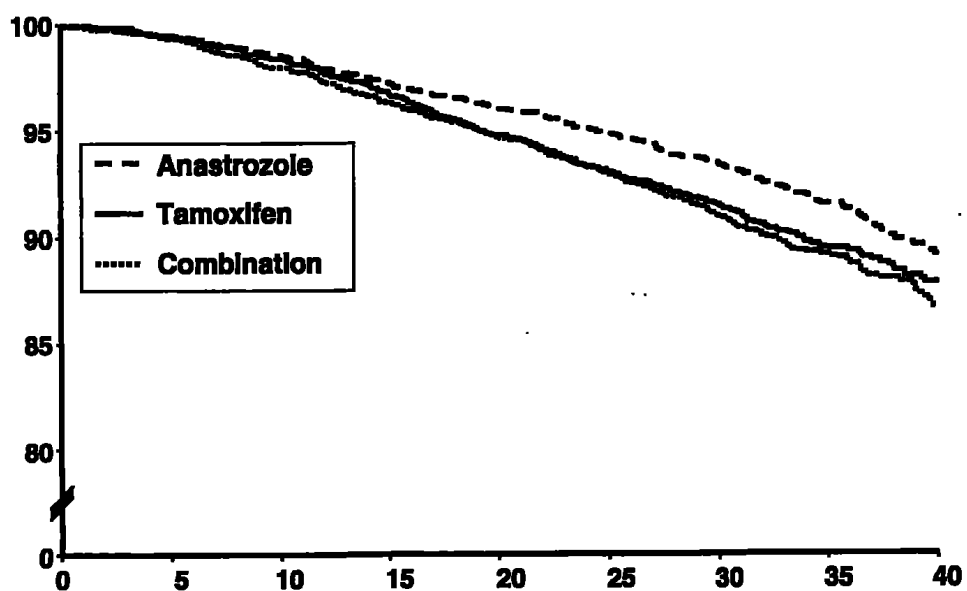


Figure 2

[Handwritten signature]

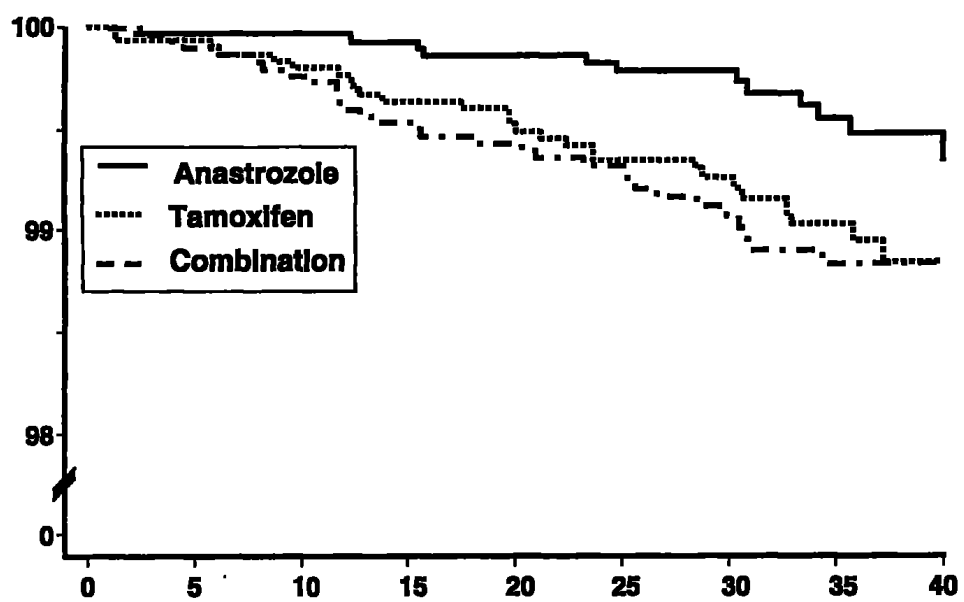


Figure 3

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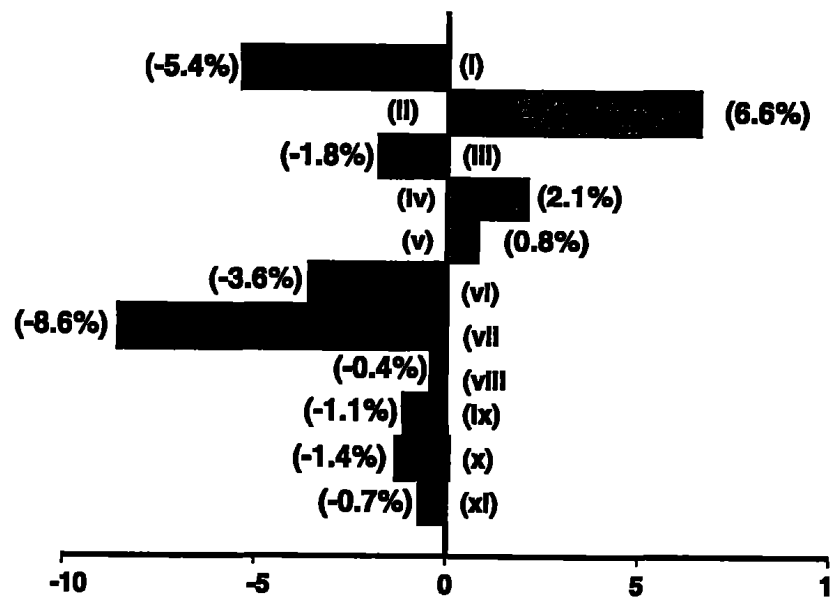


Figure 4

INTERNATIONAL SEARCH REPORT

Inventor's Application No.
PCT/GB 02/05554

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4196 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Main patent classification searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than reference documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"PHARMACOKINETICS OF ANASTROZOLE AND TAMOXIFEN ALONE, AND IN COMBINATION, DURING ADJUVANT ENDOCRINE THERAPY FOR EARLY BREAST CANCER IN POSTMENOPAUSAL WOMEN: A SUB-PROTOCOL OF THE 'ARIMIDEX AND TAMOXIFEN ALONE OR IN COMBINATION' (ATAC) TRIAL" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 85, no. 3, 3 August 2001 (2001-08-03), pages 317-324, XP009005779 ISSN: 0007-0920 the whole document -/-	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claims or which is cited to establish the publication date of another claim or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *A* document member of the same patent family

Date of the actual completion of the international search

4 Apr 11 2003

Date of mailing of the international search report

29/04/2003

Name and mailing address of the ISA

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Authorized officer

Dominguez, H

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/GB 02/05554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DOWSETT M ET AL: "The effect of anastrozole on the pharmacokinetics of tamoxifen in post - menopausal women with early breast cancer." BRITISH JOURNAL OF CANCER, (1999 JAN) 79 (2) 311-5. XP009008911 the whole document	1-9
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Y	NABHOLTZ J M ET AL: "Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial." JOURNAL OF CLINICAL ONCOLOGY, vol. 18, no. 22, 15 November 2000 (2000-11-15), pages 3758-3767, XP002236968 ISSN: 0732-183X the whole document	1-9
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Form PCT/GBA/810 (continuation of second sheet) (July 2000)

INTERNATIONAL SEARCH REPORT

Indic. of Application No.
PCT/GB 02/05554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BONNETERRE JACQUES ET AL: "Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma: Results of two randomized trials designed for combined analysis." CANCER, vol. 92, no. 9, 1 November 2001 (2001-11-01), pages 2247-2258, XP002236969 ISSN: 0008-543X the whole document	1-9
X,P	WO 02 20000 A (SLOAN KETTERING INST CANCER ;DICKLER MAURA N (US); HUDIS CLIFFORD) 14 March 2002 (2002-03-14) page 10	1,2,8,9
X,P	SAINSBURY, R. (1) ET AL: "Anastrozole is superior to tamoxifen in the treatment of post - menopausal women with early breast cancer: First results of the ATAC ('Arimidex', tamoxifen, alone or in combination) trial." INTERNATIONAL JOURNAL OF CANCER SUPPLEMENT, (2002) NO. 13, PP. 137. PRINT MEETING INFO.: 18TH UICC INTERNATIONAL CANCER CONGRESS OSLO, NORWAY JUNE 30-JULY 05, 2002 , XP002236970 the whole document	1-9
X,P	DUFFY, S. (1) ET AL: "The ATAC ('Arimidex', tamoxifen, alone or in combination) early breast cancer trial in postmenopausal patients: Endometrial sub-protocol results." INTERNATIONAL JOURNAL OF CANCER SUPPLEMENT, (2002) NO. 13, PP. 137-138. PRINT. MEETING INFO.: 18TH UICC INTERNATIONAL CANCER CONGRESS OSLO, NORWAY JUNE 30-JULY 05, 2002 , XP002236971 the whole document	1-9

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INTERNATIONAL SEARCH REPORT

Intern of Application No
PCT/GB 02/05554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	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, XX, XX, vol. 359, no. 9324, 22 June 2002 (2002-06-22), pages 2131-2139, XP004366986 ISSN: 0140-6736 the whole document	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05554

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

18
X
Inventor Application No
PCT/GB 02/05554

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0220000	A	14-03-2002	AU WO	8702801 A 0220000 A2	22-03-2002 14-03-2002

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación Internacional
3 de julio de 2003 (03.07.2003)

(10) Número de Publicación Internacional

PCT

WO 03/053438 A1

- (51) Clasificación Internacional de Patentes⁷: A61K 31/4198, A61P 35/00 (74) Agente: ASTRAZENECA; Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB)
- (21) No. Solicitud Internacional: PCT/GB02/05554
- (22) Fecha de Presentación Internacional:
8 de diciembre de 2002 (08.12.2002)
- (25) Idioma de Presentación: Inglés
- (26) Idioma de Publicación: Inglés
- (30) Datos relativos a la Prioridad:
0129457.8 10 de diciembre de 2001 (10.12.2001) GB
- (71) Solicitante (para todos los países destinatarios con excepción de MG, US): ASTRAZENECA AB [SE/SE]; Sodertälje, S-161 85 (SE).
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- (72) Inventores, e
- (75) Inventores/Solicitantes (para US únicamente): PLOURDE, Paul [US/US]; 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850 (US). ROGERS, Anthony [US/US]; 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850 (US). VOSSE, Brent [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). DUKES, Michael [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).
- (81) Países designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Países designados (regional): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurselática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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— con informe internacional de búsqueda
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- Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

(84) Título: USO DEL ANASTROZOL PARA EL TRATAMIENTO DE MUJERES POSMENOPÁUSICAS QUE TIENEN CÁNCER PRECOZ DE MAMA

(87) Extracto: La invención provee el uso del anastrozol, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para la reducción de la tasa de recurrencia de cáncer en una mujer que tiene cáncer precoz de mama. La invención provee además el uso del anastrozol, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para la reducción de la tasa de un nuevo tumor primario contralateral en una mujer posmenopáusica, que tiene cáncer precoz de mama.

WO 03/053438 A1

USO DE ANASTROZOL PARA EL TRATAMIENTO DE MUJERES POSMENOPÁUSICAS QUE TIENEN CÁNCER PRECOZ DE MAMA

En mujeres posmenopáusicas, el citrato de tamoxifeno antiestrógeno (NOLVADEX™) ha adquirido aceptación como tratamiento estándar de primera línea de cáncer avanzado de mama. Más aún, una cifra superior a 34.000 mujeres han participado en estudios clínicos de tamoxifeno complementario luego de la cirugía primaria. El efecto antineoplásico del citrato de tamoxifeno (a partir de este momento, "tamoxifeno") se relaciona con su capacidad de competir con el estrógeno por sitios de fijación en tejido objetivo tal como la mama. Adicionalmente, posee una variedad de otros mecanismos complicados que pueden mediar su efecto, incluida la inducción de transformar el factor de crecimiento beta de fibroblastos de estromas, la reducción en niveles circulantes del factor de crecimiento 1 similar a la insulina, la inhibición de angiogénesis y la inducción de apoptosis. No obstante, el estado del receptor de estrógeno (ER) del tumor sigue siendo todavía un predictor potente de respuesta.

En enfermedad avanzada, aproximadamente el 70% de los pacientes que son positivos de ER y receptor de progesterona (PR) responderán al tamoxifeno, comparado con <10% de los pacientes que son negativos ER y PR (Muss, 1992 Cáncer de mama Research and Treatment 21:51-26). En el escenario del complementario, el estado ER del tumor primario es menos discriminatorio y la última sinopsis del Grupo Cooperativo de los Participantes en el Estudio de Cáncer Precoz de Mama (EBCTCG) [Lancet 351: 1451-1467] ha sugerido que sólo pacientes negativos ER, premenopáusicos, tienen poca probabilidad de beneficiarse del tamoxifeno complementario. Es probable que otros enfoques endocrinos al tratamiento complementario del cáncer precoz de mama, que implican reducir el nivel de estradiol circulante (supresión ovárica e inhibición de aromatasa), sean dependientes de un mecanismo de receptor de estrógeno intacto en los sitios de enfermedad metastásica.

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Los inhibidores de aromatasa constituyen una clase de compuestos que actúan sistemáticamente para inhibir la síntesis del estrógeno en los tejidos. Estos compuestos impiden la biosíntesis del estrógeno inhibiendo la enzima aromatasa, que cataliza la conversión de andrógenos suprarrenales (androstenediona y testosterona) en estrógenos (estrógeno y estradiol). Por lo tanto ha habido interés en desarrollar estos compuestos como terapias potenciales de cáncer de mama sensible a hormonas en mujeres posmenopáusicas.

Aminoglutetimida fue el primer inhibidor de aromatasa en ser aprobado para el tratamiento de cáncer de mama y posee eficacia comprobada en mujeres posmenopáusicas con cáncer de mama avanzado (Stuart-Harris et al 1984, Acta Oncology 27: 721-728). Un uso más amplio del medicamento se ha visto limitado por su falta de especificidad, con el resultado de un requerimiento de administración concomitante de corticosteroides, y la ocurrencia de efectos secundarios molestos (Wells et al 1978, Annals Surgery 187: 475-487). En consecuencia, la investigación se ha centrado en el desarrollo de inhibidores de aromatasa con una mayor especificidad y un mejor perfil de tolerabilidad.

El ARIMIDEX™ (anastrozol) es un inhibidor de aromatasa no esteroide que es altamente selectivo, bien tolerado y es efectivo en tratar cáncer de mama avanzado (Buzdar et al 1995, The Breast 4(3): 256-257 Abs. 104; Jonat et al 1995, European Journal of Cancer 32A (3): 404-412; Plourde et al 1995, Journal of Steroid Biochemistry 53:175-179). (Más información sobre la experiencia clínica con el Arimidex puede encontrarse en el folleto informativo de prescripción para el Arimidex). El anastrozol se describe en la Patente de los Estados Unidos RE 366717, que se incorpora aquí por referencia.

El uso de terapias sistémicas complementario es luego del tratamiento local de cáncer de mama (cirugía con o sin radioterapia) ha tenido como resultado un aumento en la supervivencia libre de enfermedad y supervivencia general (EBCTCG, 1992, Lancet 339: 1-15, 71-85). El tamoxifeno es actualmente el agente favorito como terapia endocrina

complementario para cáncer de mama. Pacientes tratados con tamoxifeno complementario durante dos años o más pueden esperar una reducción anual en la recurrencia del 39% y una reducción anual en la mortalidad del 24%, en la ausencia de quimioterapia concomitante (EBCTCG, 1992). En mujeres premenopáusicas con tumores positivos del receptor estrógeno, el beneficio es equivalente al de mujeres posmenopáusicas, pero parece menor para mujeres premenopáusicas ER negativas. En contraste, obtendrán un beneficio mujeres posmenopáusicas tanto ER positivas como ER negativas, aunque existe una sugerencia de que entre mayor sea el nivel ER en el tumor primario, mayor será la probabilidad de beneficio.

La terapia con tamoxifeno proporciona además otros efectos benéficos, que se relaciona con la acción agonística parcial del medicamento. Éstos incluyen efectos reductores del colesterol (Love et al 1994, Journal of the National Cancer Institute 86: 1534-1539), efectos cardioprotectores (McDonald et al 1995, British Medical Journal 311: 977-980) y protección contra osteopenia (Love et al 1992, New England Journal of Medicine 326: 852-856). Sin embargo, se asocian también reacciones adversas con el tamoxifeno, que pueden clasificarse como consecuencias de la acción antiestrógena del medicamento, verbigracia sofocos, sangrado o secreción vaginal o sequedad, o efectos más generales, por ejemplo intolerancia gastrointestinal, crecimiento acentuado del tumor, inadvertencia, erupción cutánea.

Asimismo se ha reportado una incidencia creciente del cáncer endometrial en asociación con el tratamiento con tamoxifeno. La incidencia y tipo de este aumento sugieren que el mecanismo subyacente puede estar relacionado con las propiedades estrogénicas del tamoxifeno. También se han reportado los fibroides uterinos y otros cambios endometriales, incluidos hiperplasia y pólipos, en pacientes que reciben tamoxifeno.

No obstante los buenos resultados obtenidos con el tamoxifeno como una terapia complementaria en pacientes con cáncer precoz de mama, hay un buen fundamento para evaluar modalidades endocrinas alternativas en



esta población de pacientes sola, aunque pudiera pronosticarse que terapias de combinaciones podrían ser más efectivas. Los beneficios podrían incluir una duración más prolongada de la efectividad y posible libertad de las reacciones adversas asociadas con las propiedades agonistas parciales del tamoxifeno.

Una combinación posible es una combinación de anastrozol y tamoxifeno a la luz de la probada eficacia del anastrozol en cáncer avanzado de mama, su tolerabilidad favorable y un mecanismo de acción distinto del tamoxifeno.

Un estudio anterior, usando el inhibidor de aromatasas aminoglutetimida solo, demostró mejoras en la supervivencia libre de recaída y la supervivencia general, cuando comparado con placebo (Coombes et al, 1987, Cancer Research 47, 2494-2497), pero la gestión de soporte requerida, y la aceptabilidad restringida del paciente impidieron el desarrollo posterior. En contraste, el anastrozol, en estudios de fase III para el tratamiento de segunda línea de cáncer avanzado de mama, no sólo demostró una eficacia similar al acetato de megestrol, sino también un perfil favorable de tolerabilidad, especialmente con respecto a la aumento de peso.

NOLVADEX™ y ARIMIDEX™ son marcas registradas y son propiedad del grupo AstraZeneca de compañías.

Sorpresivamente hemos encontrado que el anastrozol es eficaz y bien tolerado en el tratamiento complementario de cáncer de mama, pero aún más sorprendentemente hemos encontrado que el anastrozol es significativamente más efectivo que el tamoxifeno para supervivencia libre de enfermedad en cáncer precoz de mama. Así, de acuerdo con un primer aspecto de la invención se provee aquí un método de reducir la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol, o su sal farmacéuticamente aceptable, a dicha mujer.

De acuerdo con una característica adicional del primer aspecto de la invención se provee el uso de anastrozol, o una sal farmacéuticamente



aceptable del mismo, en la preparación de un medicamento para la reducción de la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama.

En mujeres que están recibiendo tratamiento complementario para cáncer de mama, el cáncer puede resurgir en la misma mama que el cáncer original o puede ocurrir en la otra mama, denominado cáncer contralateral de mama. Sorprendentemente también hemos descubierto que el anastrozol fue significativamente más efectivo que el tamoxifeno en términos de incidencia de cáncer contralateral de mama; en consecuencia, de acuerdo con un segundo aspecto de la invención se provee aquí un método de reducir el índice de un nuevo tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol, o su sal farmacéuticamente aceptable, a dicha mujer.

De acuerdo con una característica adicional del segundo aspecto de la invención se provee el uso de anastrozol, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para la reducción del índice de un tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama.

El tamoxifeno ha sido aprobado para uso de terapia complementario para cáncer precoz de mama y, en consecuencia, podría esperarse que el anastrozol sería sinérgico con el tamoxifeno, eliminando el receptor de estrógeno de su ligando natural, permitiendo simultáneamente que el tamoxifeno ejerza su efecto benéfico mediante mecanismos biológicos alternativos. Sin embargo, sorprendentemente, hemos encontrado que en lugar de ser más efectivo que el tamoxifeno solo, una combinación de anastrozol y tamoxifeno fue sólo equivalente a tamoxifeno y significativamente peor que el anastrozol solo para tratamiento complementario de cáncer precoz de mama. Por consiguiente, sorprendentemente el tamoxifeno reduce la eficacia del anastrozol para el tratamiento complementario del cáncer precoz de mama. Por consiguiente, de acuerdo con un tercer aspecto de la invención se provee un método de

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reducir la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol o su sal farmacéuticamente aceptable a dicha mujer, en donde el anastrozol o su sal farmacéuticamente aceptable se administra en la ausencia sustancial de tamoxifeno.

De acuerdo con una característica adicional del tercer aspecto de la invención se provee el uso de anastrozol o una sal farmacéuticamente aceptable del mismo, sustancialmente en la ausencia de tamoxifeno en la preparación de un medicamento para la reducción de la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama.

La expresión 'sustancialmente en la ausencia de tamoxifeno' significa que el anastrozol se administra al paciente en la ausencia de tamoxifeno. Las pacientes que reciben terapia complementario para cáncer precoz de mama tienden a haber recibido previamente tratamiento de tamoxifeno. Por consiguiente, esta expresión se refiere a la medicación del anastrozol antes que al paciente que se está tratando.

Sorprendentemente hemos hallado además que la combinación de anastrozol y tamoxifeno fue solamente equivalente a tamoxifeno y significativamente peor que el anastrozol solo en la prevención de cáncer contralateral de mama. Así, de acuerdo con un cuarto aspecto de la invención se provee un método de reducir el índice de un nuevo tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol o su sal farmacéuticamente aceptable a dicha mujer, en donde el anastrozol o su sal farmacéuticamente aceptable se administra en la ausencia sustancial de tamoxifeno.

De acuerdo con una característica más del cuarto aspecto de la invención se provee el uso de anastrozol o una sal farmacéuticamente aceptable del mismo sustancialmente en la ausencia de tamoxifeno en la preparación de un medicamento para la reducción del índice de un nuevo tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama.

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En cada aspecto de la invención el anastrozol, o su sal farmacéuticamente aceptable se administra preferiblemente como un complementario de cirugía, quimioterapia o radiación. La cirugía incluye lumpectomía, quadrantectomía o mastectomía.

En otro aspecto de la invención, el anastrozol o su sal farmacéuticamente aceptable se administra a una mujer que tiene cáncer precoz de mama y la mujer es positiva de receptor de estrógeno o positiva de receptor de progesterona, más preferiblemente positiva de receptor de estrógeno, muy preferiblemente positiva de receptor de estrógeno y positivo de receptor de progesterona.

El anastrozol puede administrarse con una dosis entre 0.1 y 10 mg/día, preferiblemente, entre 0.5 y 5mg/día, muy preferiblemente el anastrozol se administra en 1 mg/día.

Como se describe más arriba en un aspecto de la invención el anastrozol, o su sal farmacéuticamente aceptable, se administra en la ausencia sustancial de tamoxifeno. Sin embargo, en una característica adicional del aspecto tercero y cuarto de la invención el anastrozol se administra en la ausencia sustancial de un agente antiestrógeno tal como arzoxifeno, tamoxifeno, fulvestrant, lasofoxifeno, raloxifeno, toremifeno, trilostane o TSE 424, preferiblemente en la ausencia de tamoxifeno.

Se prefiere el tratamiento de mujeres posmenopáusicas como se describe arriba; no obstante, también se contempla de mujeres premenopáusicas.

En un aspecto de la invención, la administración se lleva a cabo continuamente, durante un año por lo menos, preferiblemente durante un mínimo de dos años. El más preferido es el tratamiento continuo de cinco años, aunque también se contempla un tratamiento de más de cinco años.

Al llevar a cabo los métodos de la presente invención, el anastrozol puede suministrarse en diferentes formulaciones tal como parental (verbigracia suspensiones acuosas u oleosas) u oralmente (verbigracia, tabletas, polvos, cápsulas, gránulos, suspensiones acuosas u oleosas). Preferiblemente el anastrozol se provee en formulaciones disponibles

oralmente, preferiblemente en formulaciones que tienen de 1 a 10mg de anastrozol, muy preferiblemente 1mg. En el estudio descrito a continuación, se emplearon tabletas de 1mg.

La invención se ilustrará ahora con referencia al siguiente ejemplo no limitante y las siguientes figuras y tablas. En esta figura la leyenda HR es la abreviatura de índice de riesgo. Los valores en donde el índice de riesgo es menor de 1.00 significan que los valores están a favor del anastrozol o la combinación de anastrozol y tamoxifeno como apropiados. Los valores en donde el índice de riesgo es mayor que 1.00 significan que los valores están a favor del tamoxifeno. El 'tiempo a acontecimientos' es el tiempo entre el comienzo de recibir la terapia en el estudio y el diagnóstico de recurrencia de cáncer de mama. Figuras 1-3 describen Curvas Kaplan-Meier que serían familiares al experto; no obstante, puede hallarse más información en Modelling Survival Data in Medical Research by D.Collett (Published by Chapman & Hall, 1994). Figura 1 – Curvas Kaplan-Meier de supervivencia libre de enfermedad en población ITT.

La Figura muestra 'Tiempo a acontecimientos (meses)' en el eje X y 'Proporción de pacientes libres de acontecimiento (%)' en el eje Y.

	HR	95.2% CI	valor p
anastrozol vs tamoxifeno	0.83	0.71-0.96	0.0129
combinación vs tamoxifeno	1.02	0.88-1.18	0.7718

Esta figura muestra que en la población general, el anastrozol es superior al tamoxifeno con una reducción significativa en la tasa de recurrencia de la enfermedad, la combinación es similar a la del tamoxifeno para la población general.

Figura 2 – Curvas de Kaplan-Meier de la supervivencia libre de enfermedad en población positiva de receptor. La Figura muestra el 'Tiempo a acontecimientos (meses)' en el eje X y la 'Proporción de pacientes libres de acontecimiento (%)' en el eje Y.

	HR	95.2% CI	valor p
anastrozol vs tamoxifeno	0.78	0.65-0.93	0.0054
combinación vs tamoxifeno	1.02	0.87-1.21	0.7786

Estas figuras muestran que en la población general, el anastrozol es superior al tamoxifeno con una reducción significativa en la tasa de recurrencia de la enfermedad; la combinación es similar a la del tamoxifeno para la población general.

Figura 3 –Análisis de la incidencia de nuevos primarios de mama (contralateral);

La figura muestra el 'Tiempo al primer primario nuevo contralateral (meses)' en el eje X y la 'Proporción sin cáncer contralateral de mama (%)' en el eje Y.

	HR	95.2% CI	valor p
anastrozol vs tamoxifeno	0.42	0.22-0.79	0.0068
combinación vs tamoxifeno	0.84	0.51-1.40	0.5132

Esta figura muestra que la superioridad del anastrozol es también evidente en términos de la incidencia de cáncer primario de mama nuevo (contralateral), relativa al tamoxifeno, mientras que la combinación es similar al tamoxifeno.

Figura 4 – Diferencias significativas en reacciones adversas predefinidas entre el anastrozol y el tamoxifeno, expresadas como porcentaje. Reacciones adversas menos prevalentes en el anastrozol se muestran en el lado izquierdo de la figura y reacciones adversas menos prevalentes con el tamoxifeno se muestran a la derecha de la figura. Las reacciones adversas son las siguientes:

- (i) Sofocos
- (ii) Trastornos musculoesqueléticos
- (iii) Aumento de peso (proporción con $\geq 10\%$ de aumento en peso corporal de la línea base en el año 2)

- (iv) Fracturas de cualquier hueso
- (v) Fracturas de cadera, columna vertebral, muñeca (estas fracturas son indicadores de osteoporosis)
- (vi) Sangrado vaginal
- (vii) Flujo vaginal
- (viii) Cáncer endometrial
- (ix) Accidentes cardiovasculares isquémicos
- (x) Sucesos tromboembólicos venosos
- (xi) Trombosis de vena profunda

Esta figura muestra que el anastrozol es bien tolerado y que no se presentaron preocupaciones inesperadas de seguridad en el programa complementario.

Tabla 1 – Sumario de las características de los pacientes en el estudio;

Tabla 2 – Sumario de las características de enfermedad de los pacientes en el estudio; y

Tabla 3 – Primeras reacciones en la población ITT.

Abreviaturas: CI – intervalo de confianza;
HR – índice de riesgo;
ITT – intención de tratar;
od – una vez al día; y
OR- índice de probabilidad.

Se diseñó y condujo un estudio para comparar la eficacia y la seguridad del tamoxifeno y el anastrozol solos y con el anastrozol y el tamoxifeno en combinación como tratamiento complementario para mujeres posmenopáusicas con cáncer precoz de mama, quienes habían concluido su terapia primaria. El estudio se diseñó para comparar el tamoxifeno (20mg una vez al día [od]) y el anastrozol (1mg od) y para comparar el tamoxifeno (20mg od) y la combinación del anastrozol (1mg od) más el tamoxifeno (20mg od) como tratamiento complementario en términos de:

- a) Tiempo a la recurrencia de cáncer de mama (definido recurrencia local o distante, nuevo cáncer primario de mama, o muerte, la primera que

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ocurra); y

b) Seguridad y reacciones adversas.

Objetivos secundarios de este estudio eran comparar (i) el tamoxifeno y el anastrozol y (ii) comparar el tamoxifeno y la combinación del anastrozol más el tamoxifeno como complementario en términos de:

- a) Tiempo a la recurrencia distante;
- b) Supervivencia; y
- c) Incidencia de nuevos primarios de mama.

Específicamente, el estudio se diseñó como un estudio aleatorio, doble ciego, multicentro para comparar la eficacia y la seguridad del tamoxifeno solo, el anastrozol solo y el anastrozol en combinación con el tamoxifeno como tratamiento complementario para cáncer de mama en mujeres posmenopáusicas. Las pacientes que satisfacían los criterios de elegibilidad se distribuyeron aleatoriamente sobre una base 1:1:1 en uno de tres programas de tratamiento oral para recibir uno de los siguientes:

- a. activo anastrozol 1mg una vez diariamente más placebo de tamoxifeno una vez diariamente;
- b. activo tamoxifeno 20mg una vez diariamente más placebo de anastrozol placebo una vez diariamente;
- c. activo anastrozol 1mg una vez diariamente en combinación con activo tamoxifeno 20mg una vez diariamente.

Las pacientes se evaluaron al ingreso, 3 meses, 6 meses y, a partir de entonces, a intervalos de 6 meses. Las pacientes se reclutaron de 381 centros y en 21 países. Las pacientes se reclutaron entre julio de 1996 y marzo de 2000. Nueve mil trescientas sesenta y seis pacientes (9.366) ingresaron al estudio, y se les administraron los medicamentos en la siguiente forma: 1) Anastrozol (n=3125), 2) tamoxifen (n=2116) y 3) combinación (n=3125).

Con el fin de ser elegible para ingreso al estudio las pacientes tenían que cumplir todas las siguientes condiciones:

- a) pacientes con cáncer de mama invasivo, operable, demostrable histológicamente;

b) pacientes que hubieran concluido la totalidad de cirugía primaria y quimioterapia (si se daba el caso), y ser candidatas para recibir terapia complementario hormonal; y

c) mujeres definidas como posmenopáusicas de acuerdo con uno o más de los siguientes:-

(i) con edades de 60 o más

(ii) con edades de 45-59 años y que satisficieran uno o más de los siguientes criterios:

- amenorrea durante un mínimo de 12 meses y útero intacto;
- amenorrea durante menos de 12 meses y hormona folículo estimulante (FSH) en el rango posmenopáusico;

incluidas:

- pacientes que hubieran tenido histerectomía;
- pacientes que hayan recibido terapia de sustitución hormonal (HRT);
- pacientes que se volvieron amenorreicas mediante quimioterapia complementario (tales pacientes tienen que tener FSH medida como mínimo 6 semanas después de suspender la quimioterapia);
- ooforectomía bilateral.

Se excluyeron del estudio pacientes con cualquiera de los siguientes:

- a) pacientes en las cuales había algún indicio clínico de enfermedad metastásica;
- b) pacientes que, por cualquier razón (por ejemplo, confusión, debilidad, alcoholismo), era improbable que cumplieran los requerimientos del estudio;
- c) pacientes cuya quimioterapia se inició más de 8 semanas (es decir, 56 días) después de la conclusión de la cirugía primaria o cuya quimioterapia se concluyó más de 8 semanas (es decir, 56 días) antes de iniciar el tratamiento aleatorizado; la quimioterapia, si aplicada, debía darse posoperatoriamente, es decir, los pacientes que recibieran quimioterapia neocomplementario eran inelegibles;



- d) pacientes que no habían recibido quimioterapia y cuya cirugía primaria se hubiera concluido más de 8 semanas (es decir, 56 días) antes del tratamiento aleatorizado;
- e) pacientes que habían recibido terapia hormonal como tratamiento complementario para cáncer de mama, a menos que:-
 - a) éste se hubiera iniciado con tamoxifeno antes de la primera intervención quirúrgica y recibido durante un mínimo de 29 días; o
 - b) éste fuera terapia hormonal recibida pre-cirugía en el contexto de un estudio formal, aprobado por el Comité Directivo;
- f) pacientes que hubieran recibido tamoxifeno como parte de cualesquiera estudios de prevención de cáncer de mama;
- g) pacientes renuentes a dejar de tomar cualquier medicamento conocido por afectar el estado hormonal sexual (incluida la HRT), o en las cuales sería inapropiado;
- h) historia previa de cáncer invasivo de mama en cualquier época u otro tumor maligno invasivo en los últimos 10 años, distintos de carcinoma escamoso o basocelular de la piel o carcinoma in situ del cuello uterino, adecuadamente obtenidos mediante retiro de un pedazo de tejido con forma cónica;
- i) cualquier enfermedad concomitante grave que pondría al paciente en riesgo inusual de confundir los resultados del estudio, verbigracia un marcado historial familiar de osteoporosis, deterioro renal o hepático grave (definido como AST o ALT mayor de tres veces el límite superior del rango de referencia); o
- j) tratamiento con un medicamento no aprobado o experimental durante los 3 meses anteriores a la aleatorización;
- k) pacientes que el investigador considera que están en riesgo de transmitir cualquier infección a través de la sangre u otros fluidos corporales.

El estudio doble ciego empleó tabletas de activo y placebo de anastrozol y tamoxifeno, con el fin de mantener la incertidumbre a la terapia del estudio. Anastrozol 1 mg y el correspondiente anastrozol placebo se suministraron como tabletas blancas recubiertas con una

película. Tabletas del activo tamoxifeno 20mg y el correspondiente placebo tamoxifeno se suministraron como tabletas biconvexas, redondas, blancas.

Las pacientes se distribuyeron aleatoriamente para recibir uno de los tres regímenes de terapia oral. La dosis diaria es una tableta de anastrozol (1mg activo o placebo) más una tableta de tamoxifeno (20mg activo o placebo). Se les impartieron instrucciones a las pacientes para tomar su dosis diaria a aproximadamente la misma hora cada día. Al ingreso al estudio, las pacientes recibieron una provisión de material para 13 semanas o una provisión para 26 semanas de estudio. Las pacientes que recibieron una provisión para 13 semanas recibieron una provisión adicional para 13 semanas en la primera visita de seguimiento (3-meses). A partir de la visita a los 6 meses en adelante, las pacientes recibieron una provisión para 26 semanas. Con el fin de evaluar el cumplimiento, se les pidió a las pacientes devolver todas las tabletas no utilizadas en cada visita.

La terapia se inició lo más pronto posible después de la aleatorización, pero no más de 8 semanas luego de la conclusión de la cirugía y la quimioterapia. Las pacientes que han recibido quimioterapia primaria pueden haber iniciado el tratamiento aleatorizado hasta un máximo de 8 semanas luego de la conclusión de la quimioterapia o más pronto en las pacientes cuyos hemogramas estaban volviendo o habían vuelto a lo normal. La quimioterapia primaria tenía que haberse iniciado en las 8 semanas de concluida la cirugía primaria. Las pacientes que suspenden la quimioterapia primaria antes de la conclusión del número planeado de ciclos pueden distribuirse también aleatoriamente. Con la excepción de la terapia de estudio, se prohibió el uso de los medicamentos que afectan el estado de las hormonas sexuales o impiden la recurrencia de la enfermedad después de la aleatorización hasta la confirmación de la recurrencia de la enfermedad:-

quimioterapia citotóxica;

administración oral de cetoconazol (antifúngico) o compuestos relacionados (es decir, aplicaciones locales son aceptables);

otros tratamientos hormonales para cáncer de mama.

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Un procedimiento disponía que si las pacientes sufrían de síntomas menopáusicos serios, por ejemplo, sequedad o sangrado vaginal, sofocos, cólicos, dispareunia, debía tomarse la siguiente acción:-

- a. reportar el síntoma como una reacción adversa;
- b. si las pacientes lo querían, llevar a cabo un tratamiento aleatorizado;
- c. si era necesario, las pacientes pueden haber tomado progestinas durante 3-6 meses.

Si el tratamiento de hasta 6 meses con progestinas no controlaba los síntomas menopáusicos, pueden prescribirse HRT y/o cremas estrógenas, y puede continuar el tratamiento aleatorizado.

La siguiente información se obtuvo y evaluó del paciente:

- a) Fecha de nacimiento y origen étnico (registradas al momento del ingreso);
- b) Cualquier historia médica pasada relevante, cualquier dolencia concurrente, independientemente si la paciente había tenido o no una histerectomía, había fumado previamente o tenido HRT previa (registradas en el momento del ingreso);
- c) Toda medicación/tratamiento concomitante (registrado en el momento del ingreso);
- d) Estatura (tomada en el momento del ingreso) y peso (tomado en el momento del ingreso y hasta que la paciente suspenda el tratamiento aleatorizado);
- e) Historia de cáncer de mama – intervención quirúrgica, fecha de la cirugía, tamaño y grado del tumor primaria, estado nodal, estado ER y PR (donde se conozca), y detalles de cualquier radioterapia, quimioterapia y tamoxifeno prequirúrgico recibido (registrados en el momento del ingreso);
- f) Se realizaron las siguientes evaluaciones rutinarias de laboratorio en el momento del ingreso: hemoglobina, recuento plaquetario, leucocitos, creatinina, bilirrubina total, fosfatasa alcalina, aspartato aminotransferasa o alanina aminotransferasa, sodio, potasio y urea. Si indicado clínicamente, se realizaron otras evaluaciones de laboratorio

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hasta que la paciente suspende el tratamiento aleatorizado. Cualesquiera valores anormales clínicamente significativas debían haberse registrado como reacciones adversas, a menos que resultaran de la recurrencia de la enfermedad. Las muestras de sangre se evaluaron localmente y los impresos de laboratorio se conservaron en los registros de la clínica/hospital de la paciente.

Las pacientes se examinaron para detectar la recurrencia de cáncer de mama en todas las visitas de seguimiento, usando los siguientes criterios, que se basan en las recomendaciones del British Breast Group:-

<i>SITIO DE RECURRENCIA</i>	<i>MÉTODO DE CONFIRMACIÓN</i>
<u>LOCO-REGIONAL</u>	
1. Mama ipsilateral (incluido DCIS) *	Histología o citología
2. Pared torácica	Histología o citología
3. Nodos linfáticos axilares	Histología o citología
4. Otros nodos regionales (es decir, supraclavicular y mamario interno)	Histología o citología
<u>DISTANTE</u>	
5. Esquelético	Evaluación con ecografía CT *, o ecografía ósea con rayos x de puntos de calor. Puede ser necesaria la biopsia en el caso de una lesión única.
6. Pulmonar	Rayos x del tórax
7. Hepático	Ecografía CT o US *
8. Otro distante	Radiografía y/o biopsia. (Marcadores tumorales de crecimiento solos, por ejemplo CA 15.3, son inaceptables)

* Carcinoma Ductal In Situ

★ Tomografía computarizada
Ultrasonido

Nuevos primarios de mama (contralateral o ipsilateral) se consideraron como acontecimientos de recurrencia de enfermedad en los análisis estadísticos de tiempo a recurrencia.

El término estadístico primario del estudio fue el tiempo hasta la recurrencia de la enfermedad (recurrencia loco-regional o distante, nuevo cáncer primario de mama o muerte por cualquier causa) y seguridad/tolerabilidad. Los términos estadísticos secundarios fueron el tiempo hasta la recurrencia distante, tiempo hasta la muerte, la incidencia de nuevos primarios de mama y la incidencia de reacciones adversas predefinidas. En resumen, se hicieron dos comparaciones de tratamiento: (1) anastrozol solo comparado con tamoxifeno solo y (2) tamoxifeno solo comparado con anastrozol y tamoxifeno en combinación.

Para el tiempo hasta la recurrencia de la enfermedad, tiempo hasta la recurrencia distante y tiempo hasta la muerte, la estrategia de análisis primario incluyó todas las pacientes aleatorizadas y se realizó de acuerdo con el tratamiento aleatorizado (es decir, 'intención de tratar'), con dos componentes igualmente importantes:

- (i) Se utilizó la prueba log-rango para proporcionar una comparación básica de grupos de tratamiento sin ajustar con respecto a factores potenciales de pronóstico. (Esto es equivalente a adaptar el modelo de riesgos proporcionales Cox sin ajustar con respecto a los covariados de línea base). Se requirieron 1.056 sucesos para la significancia estadística.
- (ii) Se adaptó el modelo de riesgos proporcionales Cox, ajustando con respecto al estado del receptor de línea base, estado nodal, tamaño del tumor primario, quimioterapia previa, edad y raza. Se realizó una prueba global de interacciones, incluidas todas las interacciones de 2 vías de cada uno de estos factores de pronóstico con tratamiento aleatorizado, al nivel del 1% con el fin de evaluar si las comparaciones del tratamiento son consistentes a través de diferentes valores de los factores. También se verificó el supuesto de riesgos proporcionales con

respecto a cada factor de pronóstico usando variables dependientes del tiempo. Si había una desviación en el supuesto (al nivel del 5%), entonces debe incluirse el factor como una variable estratificada.

Las tasas de incidencia de cáncer de mama contralateral se compararon formalmente entre grupos de tratamiento aleatorizado. El análisis primario se basó en una metodología de intención de tratar.

Se realizó asimismo un análisis secundario 'por protocolo' y un análisis de subgrupo en pacientes con tumores positivos de receptor de estrógeno (ER) y/o positivos de receptor de progesterona (PR), pacientes con tumores negativos de ER y negativos de PR, y todas las demás pacientes.

Con el análisis principal, las tasas de incidencia de las siguientes reacciones adversas predefinidas se compararon formalmente entre grupos de tratamiento definidos por el tratamiento recibido: sofocos, náuseas y vómitos, astenia, alteraciones del estado de ánimo, trastornos músculo-esqueléticos, sangrado vaginal, flujo vaginal, cáncer endometrial, fracturas, cataratas, sucesos tromboembólicos venosos, y enfermedad cardiovascular isquémica. El análisis primario incluye todas las pacientes que recibieron el tratamiento de estudio, analizado de acuerdo con el tratamiento recibido. Se realizó también un análisis de subgrupo secundario, analizado de acuerdo con el tratamiento de estudio recibido, en las pacientes con tumores positivos de receptor de estrógeno (ER) y/o positivos de receptor de progesterona (PR), pacientes con tumores negativos de ER y negativos de PR, y los restantes datos de seguridad de todos los demás pacientes se resumieron y presentaron por el tratamiento recibido. Un resumen de la metodología se expone en Figura 3.

Definiciones para el análisis estadístico:

Tiempo hasta el evento (recurrencia de la enfermedad, recurrencia distante a la enfermedad, muerte) se midió desde la fecha de aleatorización. Las pacientes que no habían experimentado el evento en el momento del análisis se censuraron a la derecha en la fecha más reciente de evaluación.

Recurrencia de la enfermedad fue la primera en suceder de recurrencia local o distante, nuevo cáncer primario de mama (contralateral o ipsilateral) o

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muerte.

Recurrencia distante de enfermedad fue la primera en suceder de recurrencia distante o muerte. Fase de Enfermedad I al momento del ingreso como se definió como tumor primario de 2cm o menos en su dimensión máxima y sin indicios de implicación de nodo linfático (es decir, el número de nodos positivos es cero o cirugía axilar no era clínicamente indicada y, por lo tanto, no se realizó). Si un paciente satisfacía los criterios anteriores, se los consideraba ser Fase de Enfermedad II

Los resultados del estudio se exponen en las Figuras 1, 2, 3 y 4 y Tabla 1, 2 y 3. Los resultados se relacionan con un estudio conformado por 9.366 pacientes con una duración media de terapia de 30.7 meses con un seguimiento medio de 34.3 meses. El número total de primeros sucesos registrados, es decir, re-emergencia de cáncer de mama, fue 1.079 de los cuales 766 estuvieron en la población positiva de receptor. Los resultados muestran que el anastrozol es superior al tamoxifeno en términos de supervivencia libre de enfermedad en la población general (HR = 0.83) y en las pacientes positivas de receptor (HR = 0.78).

En consecuencia, los resultados del análisis principal del estudio indican una reducción del 17% en la tasa de sucesos de recurrencia (que incluye sucesos locorregionales, distantes, y contralaterales, así como muertes) para las pacientes que recibían anastrozol vs. aquellas que recibían tamoxifeno. En las pacientes positivas de receptor hormonal (positivas de receptor de estrógeno y/o positivas de receptor de progesterona), hubo una reducción del 22% en la tasa de recurrencia para las pacientes anastrozol vs. tamoxifeno.

Los resultados muestran asimismo que el anastrozol es superior al tamoxifeno en términos de la incidencia de cáncer contralateral de mama en la población general (OR = 0.42). Para la incidencia de nuevos tumores primarios de mama (contralaterales) las probabilidades fueron 0.42 para el anastrozol cuando comparados con el tamoxifeno (un valor de 1.00 indicaría equivalencia) en la población general.

El anastrozol fue significativamente mejor tolerado (vs. tamoxifeno)

con respecto a cáncer endometrial, sangrado vaginal, flujo vaginal, sucesos cerebrovasculares isquémicos, sucesos tromboembólicos venosos, sofocos y aumento de peso. El tamoxifeno fue mejor tolerado con respecto a trastornos musculoesqueléticos y fracturas.

Tabla 1- Características de las Pacientes

	Anastrozol (n=3125)	Tamoxifeno (n=3116)	Combinación (n=3125)
Edad media (años)	64.1	64.1	64.3
Peso medio (kg)	70.8	71.1	71.3
Estado de receptor (%)			
Positivas	83.7	83.3	84.0
Negativas	7.4	8.0	6.9
Otras	8.9	8.7	9.1
Tratamiento primario (%)			
Mastectomía	47.8	47.3	48.1
Cirugía axilar	95.5	95.7	95.2
Radioterapia	63.3	62.5	62.0
Quimioterapia	22.3	20.8	20.8
Tamoxifeno previo	1.6	1.7	1.7

Tabla 2- Características de la Enfermedad

	Anastrozol (n=3125)	Tamoxifeno (n=3116)	Combinación (n=3125)
Tamaño del tumor primario (%)			
T1 (≤ 2 cm)	63.9	62.9	64.1
T2 (>2 cm y <5 cm)	32.6	34.2	32.9
T3 (>5 cm)	2.7	2.2	2.3
Estado Nodal (%)			
Nodo + ve	34.9	33.6	33.5
Calificación (%)			
Bien diferenciado	20.8	20.5	21.2

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Moderadamente diferenciado	46.8	47.8	46.6
Poco/no diferenciado	23.7	23.3	23.7
No evaluado/registrado	8.7	8.4	8.5

Tabla 3 – Primeros Sucesos en Población ITT

	Anastrozol (n=3125)	Tamoxifeno (n=3H6)	Combinación (n=3125)
Primer suceso	317	379	383
Loco-regional	67	83	81
Distante	156	181	202
Contralateral (invasivo)	9	30	23
Contralateral (DCIS)	5	3	5
Muerte - cáncer de mama	2	1	2
Muerte - otra razón	78	81	70

Reivindicaciones

1. El uso de anastrozol, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para la reducción de la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama.
2. El uso de anastrozol, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para la reducción de la tasa de un nuevo tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama.
3. El uso de acuerdo con Reivindicación 1 o Reivindicación 2 en donde el anastrozol se suministra sustancialmente en ausencia de un agente antiestrógeno.
4. El uso de acuerdo con Reivindicación 3 en donde el agente antiestrógeno es tamoxifeno.
5. El uso de acuerdo con una cualquiera de las Reivindicaciones precedentes en donde la mujer que tiene dicho cáncer precoz de mama es positiva de receptor de estrógeno o positivas de receptor de progesterona.
6. El uso de acuerdo con Reivindicación 5 en donde la mujer que tiene dicho cáncer precoz de mama es positiva de receptor de estrógeno y positiva de receptor de progesterona.
7. El uso de acuerdo con una cualquiera de las Reivindicaciones precedentes en donde el anastrozol se provee para administración en una dosis de 1 mg/por día.

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8. Un método de reducir la tasa de recurrencia de cáncer en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol, o su sal farmacéuticamente aceptable, a dicha mujer.
9. Un método de reducir la tasa de un nuevo tumor primario contralateral en una mujer posmenopáusica que tiene cáncer precoz de mama, el cual comprende administrar una cantidad efectiva de anastrozol, o su sal farmacéuticamente aceptable, a dicha mujer.

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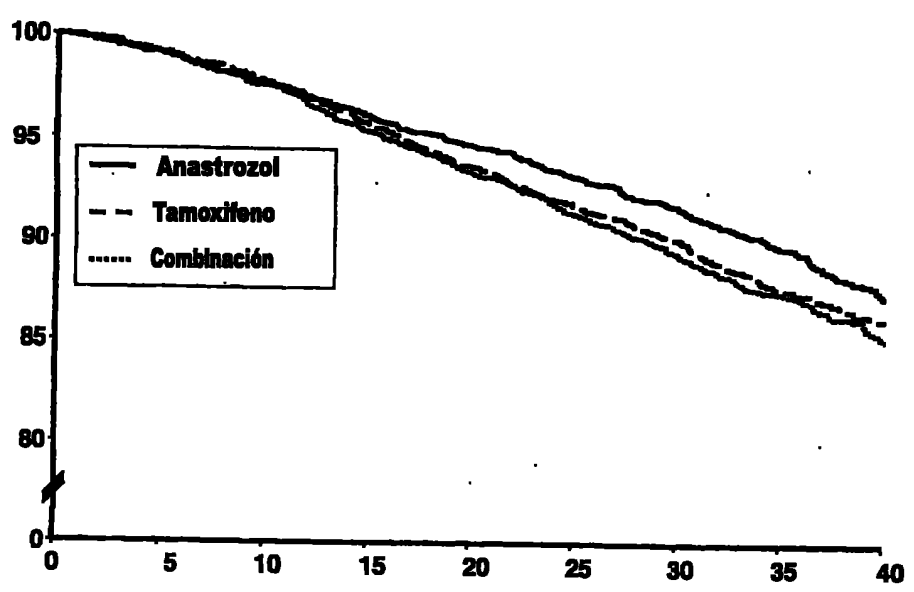


Figura 1

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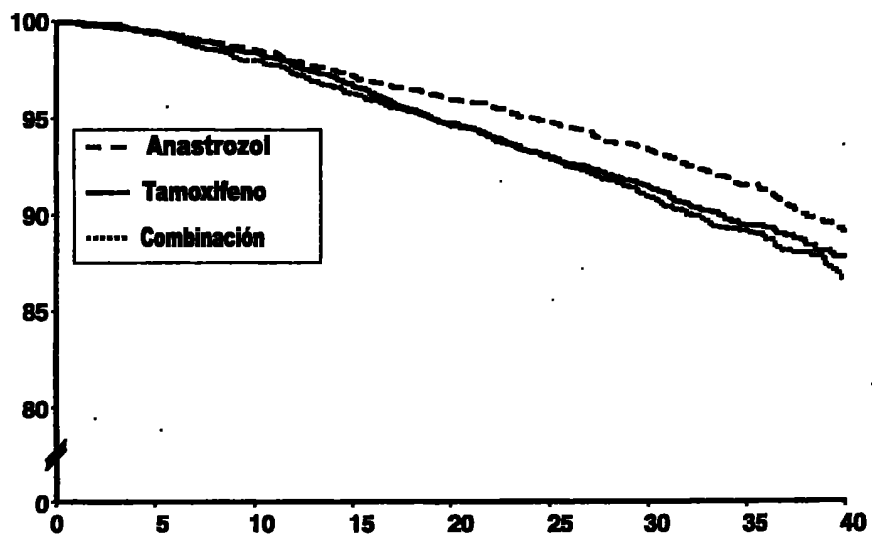


Figura 2

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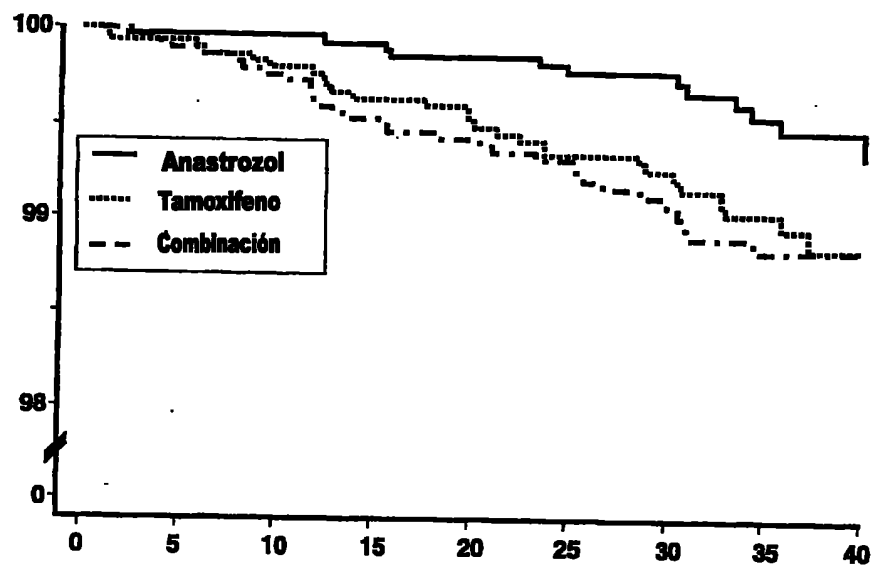


Figura 3

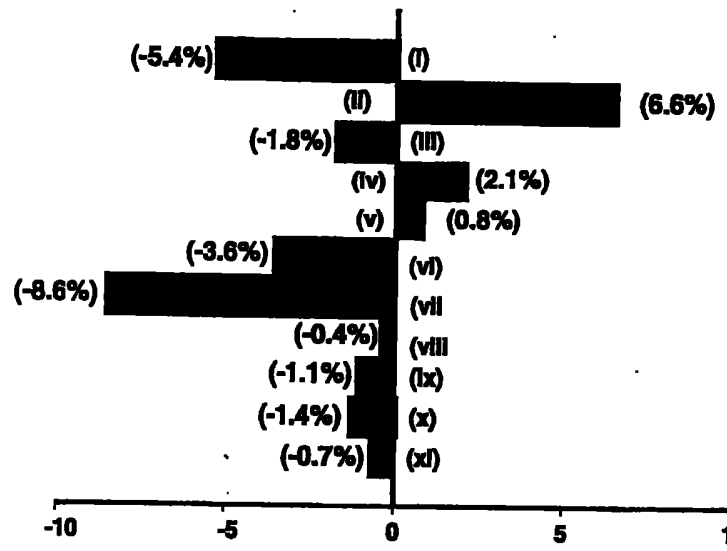


Figura 4

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PATENT COOPERATION TREATY

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NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

To:

BRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
Mercedes, Alderley Park
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GRANDE BRETAGNE

Reg. letter

Date of mailing
(day/month/year)

01/10/2003

Applicant's or agent's file reference

100600/WO

IMPORTANT NOTIFICATION

International application No.

PCT/GB 02/ 05554

International filing date (day/month/year)

06/12/2002

Priority date (day/month/year)

10/12/2001

Applicant

10 OCT 2003

ASTRAZENECA AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/

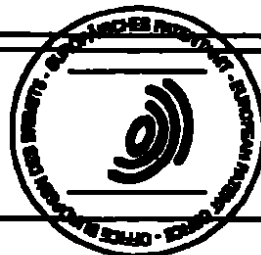


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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 100600/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 02/ 05554	International filing date (day/month/year) 06/12/2002	Priority date (day/month/year) 10/12/2001
International Patent Classification (IPC) or national classification and IPC A61K31/4196		
Applicant ASTRAZENECA AB et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

- This report contains indications relating to the following items:
 - ☒ Basis of the report
 - ☐ Priority
 - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application

Date of submission of the demand 17/06/2003	Date of completion of this report 26/09/2003
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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB 02/05554

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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PCT REQUEST

Original (for SUBMISSION) - printed on 05.12.2002 02:31:05 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	100600/WO
I	Title of invention	METHOD OF TREATMENT
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW NX SD SL SZ TZ UG ZM ZW); EA: (AM AE BY KG KZ MD RU TJ TM); EP: (AT BE BG CH LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
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PCT REQUEST

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Original (for SUBMISSION) - printed on 05.12.2002 02:31:05 PM

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100800/WO

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III-3-1	This person is:	applicant and inventor
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III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or Inventor	
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III-4-2	Applicant for	US only
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III-4-6	State of nationality	GB
III-4-7	State of residence	GB

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Original (for SUBMISSION) - printed on 05.12.2002 02:31:05 PM

100800/WO

III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	DUKES, Michael
III-5-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-5-6	State of nationality	GB
III-5-7	State of residence	GB
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
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IV-1-2	Address:	Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MX SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BE CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	10 December 2001 (10.12.2001)
VI-1-2	Number	0129457.8
VI-1-3	Country	GB
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-
VIII-5	Declaration as to non-prejudicial disclosure or exceptions to lack of novelty	-

PCT REQUEST

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	17	-
IX-3	Claims	1	-
IX-4	Abstract	1	EXABST00.TXT
IX-5	Drawings	4	-
IX-7	TOTAL	28	
Accompanying items		paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	ASTRAZENECA	
X-1-2	Name of signatory	Agent	
X-1-3	Capacity	AstraZeneca	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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54 2
The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100600/WO	
International application No. PCT/GB2002/005554	International filing date (day/month/year) 06 December 2002 (06.12.2002)	(Earliest) Priority date (day/month/year) 10 December 2001 (10.12.2001)	
Title of invention USE OF ANASTRAZOLE FOR THE TREATMENT OF POST-MENOPAUSAL WOMEN HAVING EARLY BREAST CANCER			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA AB S-151 85 Södertälje Sweden		Telephone No. +44 1625 5130148	
		Facsimile No. +48 8 553 28820	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1K 1LN GB			
State (that is, country) of nationality: GB		State (that is, country) of residence: GB	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) PLOURDE, Paul 1800 Concord Pike PO Box 15437 Wilmington, DE United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ROGERS, Anthony
1800 Concord Pike
P O Box 15437
Wilmington, DE
United States of America

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VOSE, Brent
Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DUKES, Michael
Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*BRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
Mersey, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
GB

Telephone No.

+44 1625 513228

Facsimile No.

+46 8 553 28820

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed
☐ as amended under Article 34the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34the drawings ☒ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

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received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....
BRYANT, Tracey
Global Intellectual Property, Patents, AstraZeneca AB

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1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

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Demand received from IPEA on:

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) ASTRAZENECA AB

domiciliado(s) en

domiciled in S2-131-Bodertalje, Sweden

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistirse a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistirse, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

domiciliado(s) en la Carrera 7 No. 18-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

domiciled in Carrera 7 No. 18-56 Piso 9, my (our) attorney(s) to receive and sign for me (us) all notifications and to designate and ratify judicial attorneys.

Granted and signed in Macclisfield, Cheshire,

this 10 MAR 2004 2003

Signature

Name KEVIN BILL
Title Director, IP Services

110816

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
ion fecha

que quien confiere el presente poder es su representante.

***Notario Público (sello)**

CERTIFICADO NOTARIAL

PERSONA NATURAL

dy de de , compareció(eron)
ita ml

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que preceda y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of Feb 1964 of
personally appeared before me

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

ATTORNEY
of
ATTRAENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Indiana
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public  **Ben**

**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) granted he (they) grant(s) the document for the purpose(s) therein expressed.

QUE ESTÁ
COPIA AUTÉNTICA A
BOGOTÁ D.C. REPÚBLICA DE COLOMBIA

10 MAR 2004

OSCAR ALARCON NUÑEZ

Notary Public CUAENTA Y SEIS
Notary (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

57


APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)
UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1 Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2 Has been signed by J B Hodgson
été signé par

3 Acting in the capacity of Notary Public
agissant en qualité de

4 Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5 at London/Londres
Certified/Attesté
6. the/le 17 February 2004

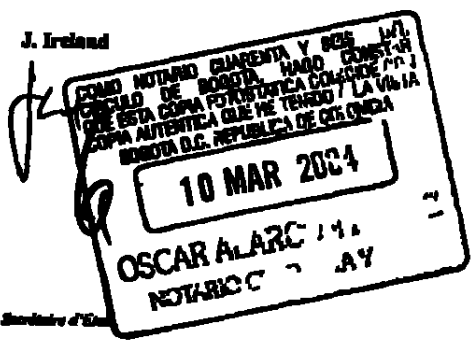
7 by Her Majesty a Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G348987**

9 Stamp
timbre



10. Signature: J. Ireland



If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961
it should be presented to the consular section of the mission representing that country

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicación de que se solicita la concesión de una patente	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
Descripción de la invención.	()	()
Dibujos de ser estos pertinentes.	()	()
Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

DISEÑO INDUSTRIAL ()		
Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()		
Indicación de que solicita el registro de un Esquema de trazado	()	()
Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
Representación gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Fecha



2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
ASTRAZENECA A.B.

Oficio N° 07394

ASUNTO:	Radicación N°	04-64979
	Solicitud internacional	PCT/GB2002/05554
	Fecha inicio fase nacional	10/07/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

□ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 06 AGO. 2004.