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(54) Titre : AGENT PERMETTANT D'ABAISSEZ LES NIVEAUX D'ENDOTHELIN
(54) Title: AGENT FOR LOWERING ENDOTHELIN LEVELS

(57) **Abrégé/Abstract:**

The present invention relates to a new medical use of triphenylethylene antiestrogen toremifene or a pharmaceutically acceptable thereof for lowering endothelin-1 levels in mammals, and for the prevention or treatment of endothelin mediated diseases.



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(21) International Application Number: PCT/FI99/01016 (22) International Filing Date: 8 December 1999 (08.12.99) (30) Priority Data: 9827121.6 9 December 1998 (09.12.98) GB (71) Applicant (for all designated States except US): ORION CORPORATION [FI/FI]; Orionintie 1, FIN-02200 Espoo (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): YLIKORKALA, Olavi [FI/FI]; Liisankatu 12 D, FIN-00170 Helsinki (FI). METSÄ-HEIKKILÄ, Merja [FI/FI]; Katrillipolku 11 C, FIN-04420 Järvenpää (FI). HIETANEN, Päivi [FI/FI]; Reserviläisentie 8, FIN-02660 Espoo (FI). ELLMEN, Juha [FI/FI]; Koukkukankareentie 40 as 4, FIN-20320 Turku (FI). (74) Agent: ORION CORPORATION; Orion Pharma, Industrial Property Rights, P.O.Box 65, FIN-02101 Espoo (FI).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: AGENT FOR LOWERING ENDOTHELIN LEVELS (57) Abstract The present invention relates to a new medical use of triphenylethylene antiestrogen toremifene or a pharmaceutically acceptable thereof for lowering endothelin-1 levels in mammals, and for the prevention or treatment of endothelin mediated diseases.		

AGENT FOR LOWERING ENDOTHELIN LEVELS

Technical field of the invention

The present invention relates to a new medical use of, and a method of
5 treatment using, toremifene or a pharmaceutically acceptable thereof, for lowering
endothelin-1 levels in mammals, and for the prevention or treatment of endothelin
mediated diseases.

Background of the invention

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Endothelin-1 (ET-1) is a 21 amino acid peptide produced by endothelial cells
in response to a variety of chemical and mechanical signals. It has a powerful
vasoconstrictor and bronchoconstrictor activity and exerts multiple biologic effects.
Another endothelium-derived mediator nitric oxide (NO) is in contrast known to be
15 potent vasorelaxing factor. Endothelin-1 (ET-1) is one of three recently identified
potent vasoconstricting peptides which also include endothelin-2 and endothelin-3.
The molecular structure and biological activities of endothelin were explored in
several studies starting soon after its discovery in 1988, but only recently has the
availability of specific ET-1 antagonists allowed its physiological activities to be
20 explored.

There is now evidence that the excess production or excess secretion of
endothelin is one of the factors responsible for e.g. systemic hypertension, pulmonary
hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress
25 syndrome, myocardial infarction, thrombosis, congestive heart failure, cardiac
hypertrophy, cerebral vasospasm, cerebral infarction, subarachnoidal haemorrhage,
vascular dementia, Raynaud's disease, renal failure, cyclosporin nephrotoxicity,
benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver cirrhosis,
pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after
30 transplantation, multiple organ failure, preeclampsia and endotoxic shock.

Thus a compound which antagonizes endothelin or inhibits the production or
secretion of endothelin has been considered to be useful in the treatment or
prevention of the above various diseases.

CONFIRMATION COPY

Toremifene and tamoxifen are triphenylethylene antiestrogens currently used in the treatment of estrogen receptor positive breast cancer. The preparation of toremifene and its salts is described in US 4,696,949. The use of toremifene for the reversal of multidrug resistance of cancer cells to cytotoxic compounds has been described in US 4,990,538. The use of toremifene for treating autoimmune diseases has been described in WO 94/09764. The use of toremifene for sensitizing cancer cells to killer cell mediated lysis is described in WO 95/04544. Finally, the use of toremifene for lowering serum lipid peroxides has been described in WO 97/41847.

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Summary of the invention

It has been found that toremifene or a pharmaceutically acceptable salt thereof is able to lower endothelin levels in mammals. Therefore toremifene or a pharmaceutically acceptable salt thereof is useful in the prevention or treatment of endothelin related conditions such as systemic hypertension, pulmonary hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress syndrome, myocardial infarction, thrombosis, congestive heart failure, cardiac hypertrophy, cerebral vasospasm, cerebral infarction, subarachnoidal haemorrhage, vascular dementia, Raynaud's disease, renal failure, cyclosporin nephrotoxicity, benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver cirrhosis, pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after transplantation, multiple organ failure, preeclampsia and endotoxic shock.

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Detailed description of the invention

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In a first aspect the present invention provides a new medical use of toremifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in lowering levels of endothelin in a patient.

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The present invention also provides a new medical use of toremifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the prevention or treatment of endothelin mediated conditions. In particular the present invention provides a new medical use of toremifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the prevention or treatment of systemic hypertension, pulmonary hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress syndrome, myocardial infarction, thrombosis, congestive heart failure, cardiac hypertrophy, cerebral vasospasm, cerebral infarction, subarachnoidal haemorrhage, vascular dementia, Raynaud's

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disease, renal failure, cyclosporin nephrotoxicity, benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver cirrhosis, pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after transplantation, multiple organ failure, preeclampsia and endotoxic shock.

In another aspect the present invention provides a method for lowering endothelin levels in a patient comprising administering to a patient in need thereof an endothelin level lowering amount of toremifene or a pharmaceutically acceptable salt thereof.

10 In another aspect, the present invention provides for use of toremifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in lowering levels of endothelin in a patient suffering from systemic hypertension, pulmonary hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress syndrome, cardiac hypertrophy, subarachnoidal haemorrhage, Raynaud's disease, renal failure, cyclosporine nephrotoxicity, benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver cirrhosis, pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after transplantation, multiple organ failure, preeclampsia or endotoxic shock.

20 In another aspect the present invention provides a method for the prevention or treatment of endothelin mediated conditions comprising administering to a patient in need thereof an endothelin lowering amount of toremifene or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for the prevention or treatment of endothelin mediated conditions selected from a group consisting of systemic hypertension, pulmonary hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress syndrome, myocardial infarction, thrombosis, congestive heart failure, cardiac hypertrophy, cerebral vasospasm, cerebral infarction, subarachnoidal haemorrhage, vascular dementia, Raynaud's disease, renal failure, cyclosporin nephrotoxicity, benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver cirrhosis, pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after transplantation, multiple organ failure,
30 preeclampsia and endotoxic shock.

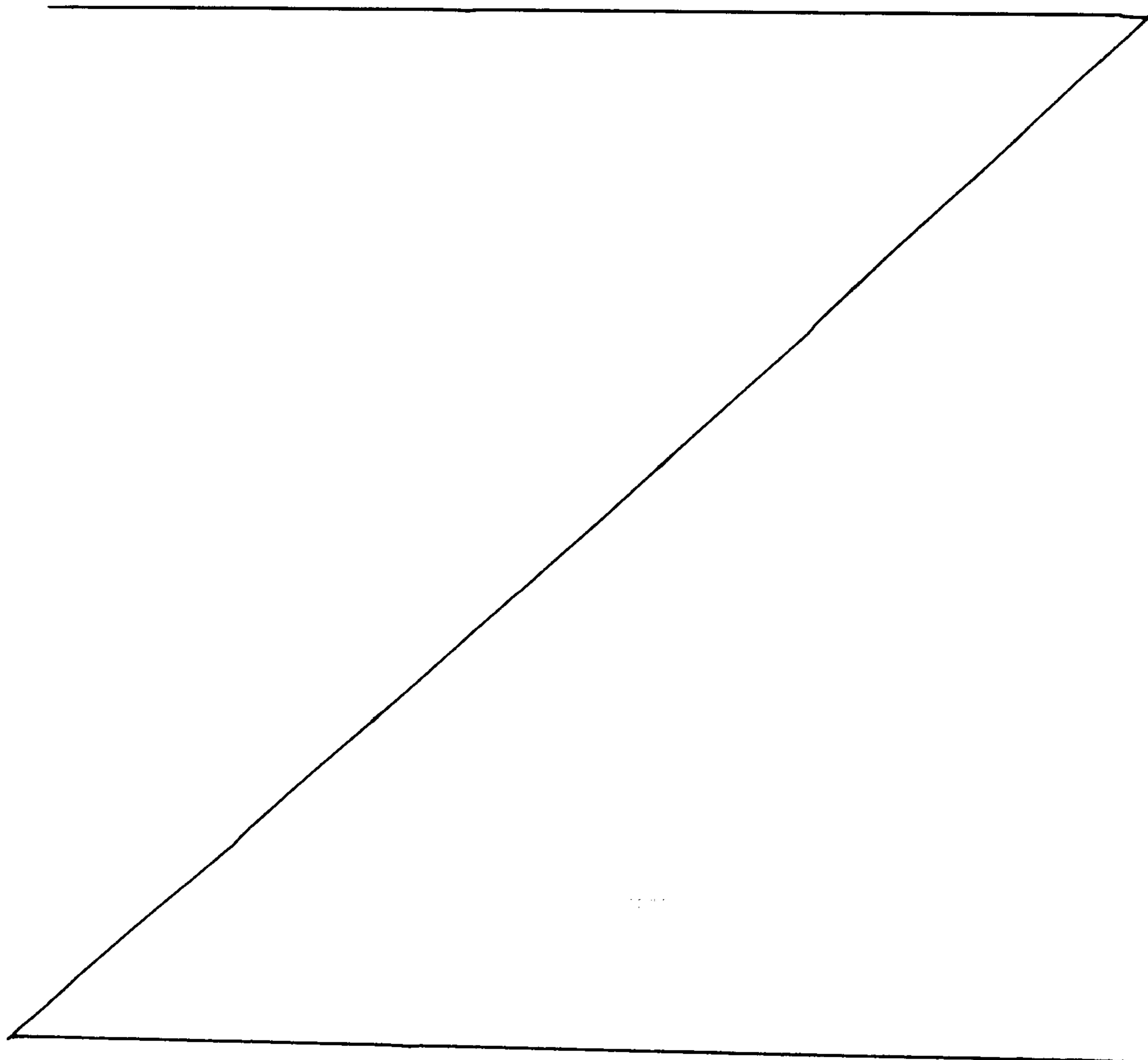
Toremifene or a pharmaceutically acceptable salt thereof may be administered in a variety of ways including orally, parenterally or transdermally using conventional forms of preparations, such as capsules, tablets, granules, powders,

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suppositories, injections, patches, suspensions and syrups. The active compound may be administered monthly, weekly or daily or several times a day depending upon the patient's needs. A typical daily oral dosage is within the range of from about 1 mg to about 500 mg, preferably from about 5 to about 100 mg, of the active compound. However, the dosage may be properly varied depending on the age, body weight and conditions of the patient as well as on the administration method. The compound of the invention may be administered alone or together with other active compounds. The term "endothelin level lowering amount" means here an amount that is capable of lowering endothelin levels systemically, e.g. in plasma, or locally, e.g. in tissue.

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The compositions according to the invention can be prepared by the methods commonly employed in the art. In addition to the active compound the compositions



may contain pharmaceutically acceptable additives commonly used in the art, such as carriers, binders, excipients, lubricants, suspending agents and diluents. The amount of the active compound in the compositions of the invention is sufficient to produce the desired therapeutical effect, for example about 1 mg to 500 mg, more preferably
5 from about 5 to about 100 mg, in unit dosage for both oral and parenteral administration.

Experiments

10 Effect of toremifene on endothelin-1 level in plasma

Postmenopausal breast cancer patients were treated with 40 mg/d toremifene (FarestonTM) (n = 19), 20 mg/d tamoxifen (TadexTM) (n = 25) or 2 mg/d estradiol valerate (ProgynovaTM)(n = 14) orally for one year. The 44 patients of the
15 antiestrogen groups had been operated on breast cancer 6-8 weeks before the trial. Plasma samples (10 ml) were collected before and at 6 and 12 months of each regimen, and plasma levels of endothelin-1 (ET-1) and nitrite/nitrate (NOx) were measured by established methods. The data (presented as mean $\pm$ SE) were analyzed by two-way analysis of variance (ANOVA) for repeated measures. When differences
20 were indicated by ANOVA, their significances at individual timepoints were calculated by means of a t-test for independent means (between-groups comparison) or a t-test for dependent means (comparison to baseline within a single group). For determination of correlation between two variables, the Pearson coefficient was calculated. The results are shown in Table 1.

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Table 1. Plasma levels of endothelin-1 (ng/l) and nitrite/nitrate ($\mu\text{mol/l}$) in breast cancer patients (ns = no significant).

		Before treatment	At 6 months	P (0-6)	At 12 months	P (0-12)
5	Endothelin-1					
	Toremifene	3.0 ± 0.2	2.6 ± 0.2	0.01	2.6 ± 0.2	0.06
	Tamoxifen	3.5 ± 0.2	3.5 ± 0.2	ns	3.2 ± 0.2	ns
10	Estrogen	2.8 ± 0.2	2.7 ± 0.2	ns	2.7 ± 0.2	ns
	Nitrite/nitrate					
	Toremifene	23.4 ± 4.0	21.0 ± 2.5	ns	21.6 ± 3.1	ns
	Tamoxifen	20.6 ± 2.3	22.8 ± 4.0	ns	20.4 ± 2.5	ns
15	Estrogen	25.8 ± 3.7	21.5 ± 3.2	ns	18.5 ± 2.7	ns

The results show that toremifene significantly lowered endothelin-1 level in patients during the treatment whereas another antiestrogen tamoxifen had no effect. No treatment led to significant changes in plasma NOx.

Occurrence of thromboses and cerebrovascular accidents

In three clinical adjuvant trials effects of oral toremifene 40 mg/d was compared to oral tamoxifen 20 mg/day for 3 years in postmenopausal breast cancer patients. The occurrence of serious deep vein thromboses and serious cerebrovascular accidents in toremifen and tamoxifen groups are summarized in Table 2.

Table 2. The occurrence of deep vein thromboses and cerebrovascular accidents in clinical adjuvant trials in postmenopausal breast cancer patients.

	Toremifene	Tamoxifen
Number of patients	1120	1110
Deep vein thromboses	7	13
Cerebrovascular accidents	2	14

The results show that clearly more vascular complications (deep vein thrombosis and cerebrovascular events) are seen among tamoxifen treated patients than among those

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treated with toremifene. This difference may be explained by the beneficial effect of toremifene on endothelin-1 levels in the patients.

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CLAIMS

1. Use of toremifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in lowering levels of endothelin in a patient suffering from systemic hypertension, pulmonary hypertension, pulmonary fibrosis, bronchial asthma, acute respiratory distress syndrome, cardiac hypertrophy, subarachnoidal haemorrhage, Raynaud's disease, renal failure, cyclosporine nephrotoxicity, benign prostatic hyperplasia, diabetic angiopathy, gastric ulcer, liver
10 cirrhosis, pancreatitis, migraine, glaucoma, retinopathy, sepsis, organ dysfunction after transplantation, multiple organ failure, preeclampsia or endotoxic shock.
2. Use according to claim 1 wherein the medicament is for lowering endothelin levels in a patient suffering from benign prostatic hyperplasia.