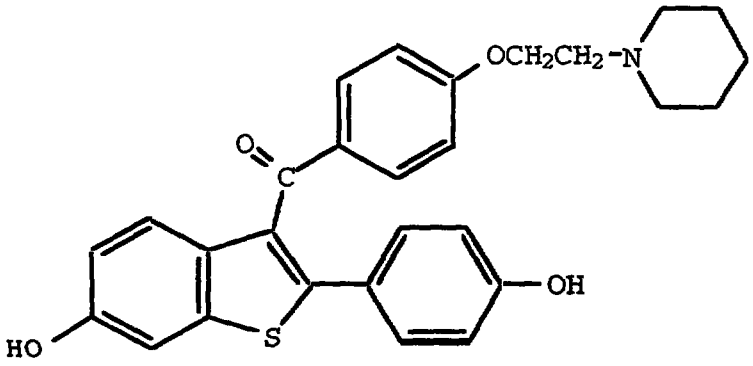
IMPROVEMENTS IN OR RELATING TO THE PROPHYLAXIS OF BREAST CANCER

This invention relates to the prophylaxis of breast cancer in women.

Breast adenocarcinoma or cancer is a major medical problem in women, particularly above the age of thirty-five. Currently in the United States, it is estimated that women have a one in eight chance of developing this disease in the course of their lifetime. Breast carcinoma is a major cause of mortality in women, as well as a cause of disability, psychological trauma, and economic loss. A large number of women contracting this disease eventually die from its effects either directly or indirectly from complications.

Raloxifene has the chemical structure:



(I)

and together with, *inter alia*, its pharmaceutically acceptable salts was first described in U.S. Patent Specification No. 4,418,068.

U.S. Patent No. 4,418,068 teaches that raloxifene is useful in the treatment of mammary tumors and in the prophylaxis of recurring benign mammary fibrocystic disease.

Unfortunately, clinical trial of raloxifene for the treatment of breast cancer did not support human efficacy. That negative result discouraged further evaluation of raloxifene as a therapeutic agent against breast cancer in humans.

Surprisingly, a chance discovery has now established that raloxifene is highly effective in the prophylaxis of breast cancer. Even more surprisingly, that protective effect has been found to manifest itself particularly strongly in a narrow dosage range.

Thus, according to one aspect of the invention, there is provided a method of inhibiting the development of breast cancer in a post-menopausal woman, which comprises administering to such a woman raloxifene, or a pharmaceutically-acceptable salt thereof, in an amount of from about 30 to from about 150 mg per day.

In a second aspect of the invention, there is provided the use of raloxifene, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament adapted for the administration of from about 30 to about 150 mg per day of said raloxifene, or said pharmaceutically-acceptable salt, to a post-menopausal woman so as to inhibit the development of breast cancer in that woman.

In a third aspect of the invention, there is provided a pharmaceutical composition for the inhibition of development of breast cancer in a post-menopausal woman, characterized in that said composition comprises sufficient raloxifene, or sufficient of a pharmaceutically-acceptable salt thereof, to provide from about 30 to about 150 mg per day of said raloxifene, or said pharmaceutically-acceptable salt of raloxifene.

In a fourth aspect of the invention, there is provided an article of manufacture comprising packaging material, and raloxifene, or a pharmaceutically-acceptable salt thereof, contained within said packaging material, wherein said packaging material comprises label directions which indicate that said raloxifene, or said pharmaceutically-acceptable salt of raloxifene, is to be

administered to a post-menopausal woman, in an amount from about 30 mg to about 150 mg per day to inhibit the development of breast cancer.

Preferably, the raloxifene, or pharmaceutically-acceptable salt thereof, should not be administered in an amount greater than 120 mg per day, more preferably not greater than 100 mg per day. The preferred lower level of administration is about 40 mg per day, more preferably about 50 mg per day. The most preferred range for prophylactic efficacy is the range from 50 to 80 mg per day, and outstanding protective effects have been observed at about 60 mg per day, for instance from 50 to 70 mg per day.

The term "inhibiting the development of breast cancer" as used herein is intended to primarily refer to a situation in which *de novo* transformation of normal breast cells to cancerous or malignant cells is inhibited. However, there may be situations in which women have clinically non-detectable cancerous cells in their breasts, and the inhibition of development of such, as yet, clinically insignificant cancers also forms part of the invention. Not included within the scope of this invention, is the therapy of existing, clinically-detectable breast cancer.

Raloxifene, and its pharmaceutically-acceptable salts can be made according to established procedures, such as those described in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635, and U.K. Patent Application 2,293,602. A preferred crystalline form is described in U.K. Patent Application No. 2,293,382, all of which are incorporated by reference herein. In general, the synthesis starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The hydroxyl groups of the starting compound are protected, the 3-position is acylated, and the product deprotected to form the desired compounds.

Raloxifene forms pharmaceutically-acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases including the physiologically

acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, ß-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. The preferred salt for use in the invention is the hydrochloride salt.

The pharmaceutically-acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers,

and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration. Whilst parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes, is a possibility, clearly for prophylaxis this is much less desirable than oral administration. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Effective daily doses of raloxifene, or pharmaceutically-acceptable salts, will be from about 30 to about 150 mg/day. Such dosages will be consumed by a subject from once to possibly three times each day. A preferred dosage range is between about 60 and about 120, or 150, mg/day, with 60 mg/day particularly preferred.

Although one would expect the prophylactic effect provided by the invention to be immediate, statistically significant data, as compared with the general population,

is most apparent where the term of administration is at least six months, preferably at least one year, most preferably at least two years. Clearly, the prevention of breast cancer is such a significant enhancement of a woman's quality of life, that very long term, even life long, therapy is advantageous.

As stated above, the preferred route of administration will be the oral route. For such purposes the following oral dosage forms are available.

Formulations

Formulation 1: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene HCl	60
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Preferred tablet formulations include the following:

Formulation 2:

Ingredient	Quantity (mg)	Function
Raloxifene HCl	60.0	Active
Spray Dried Lactose	30.0	Soluble Diluent
Anhydrous Lactose	12.0	Soluble Diluent
Povidone	12.0	Binder
Polysorbate 80	2.4	Wetting Agent
Crospovidone	14.4	Disintegrant
Magnesium Sterate	1.2	Lubricant
(Core Tablet Weight	240.0)	
Film Coating		
Color Mixture White	12.0	Coloring Agent
Talc	trace	Polishing Aid
Carnauba Wax	--	Polishing Aid

Formulation 3:

Ingredient	Quantity (mg)	Function
Raloxifene HCl	60.0	Active
Spray Dried Lactose	29.4	Soluble Diluent
Anhydrous Lactose	120.0	Soluble Diluent
Povidone	12.0	Binder
Polysorbate 80	2.4	Wetting Agent
Crospovidone	14.4	Disintegrant
Magnesium Sterate	1.2	Lubricant
(Core Tablet Weight	240.0)	
Film Coating		
Color Mixture White	12.0	Coloring Agent
Talc	--	Polishing Aid
Carnauba Wax	trace	Polishing Aid

TEST PROCEDURE

The results of clinical studies with raloxifene (in the form of the hydrochloride salt) are now presented to illustrate the protective effect of the invention.

The principal design was double-blind randomized, and placebo-controlled in approximately 7500 post-menopausal women. The studies generally had three groups (arms) of patients assigned randomly to placebo, 60 mg of drug per day, or 120 mg of drug per day, enrolled in equal numbers per group, all via the oral route.

Patients selected for these studies were post-menopausal women (2+ years since the last menstrual period) between the ages of approximately fifty to eighty years old. In addition, those women were in generally good health, as appropriate for their age.

Exclusion criteria from participating in this study included past or present cancer. In particular, no woman was allowed to participate in the study who currently had or was suspected to have a history of, breast carcinoma or other estrogen-dependent neoplasia. This exclusion criterion generated a population of patients which reflected that of the general population in regard to the potential for developing breast cancer.

Potential patients were screened prior to enrollment into the study. Patients were required to reveal current medical conditions and histories. All potential patients were required to have either a baseline mammogram or breast ultrasound evaluation - to screen for the presence of breast cancer. If there was some reason for a patient to leave the study, and breast cancer was or might be expected, this patient would receive a breast cancer evaluation. The diagnosis of breast cancer was made histopathologically from biopsy or surgical specimens.

The results shown in Table I are for patients who were found through various diagnostic methods, including the one year mammogram results, to have breast adenocarcinoma, or

cancer. These patients were immediately discontinued from study participation and their status unblinded to reveal the therapy (arm) to which they had been randomized.

The number of patients in each arm of the study was 5078 on the combined two dosage levels of raloxifene and 2539 on placebo.

Table I

Patient No.	Treatment Group	No.of Months
4053	Placebo	5
3057	Placebo	12
6637	Placebo	12
2233	Placebo	1
2652	Placebo	4
7666	Placebo	3.5
3994	Placebo	2
4678	Placebo	6
6018	Placebo	15
3817	Placebo	13
1858	Placebo	13
0238	Placebo	3
3930	60 mg Raloxifene	11
2693	120 mg Raloxifene	4
5801	120 mg Raloxifene	4
0393	120 mg Raloxifene	4
0032	120 mg Raloxifene	12

The results of the data indicate that the relative risk for the patients in this study of being diagnosed as having breast cancer was 1.0 (by definition) for placebo and 0.21 (95% confidence interval, 0.07 to 0.59) for those taking raloxifene (data on patients for both the 60 mg and 120 mg doses were pooled), as compared with placebo. The 60 mg dose was more favorable and is therefore a preferred embodiment of the current invention.

When all pertinent studies on raloxifene were combined, a total of 14 placebo-arm patients incurred breast

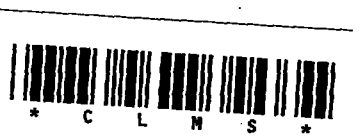
cancer, while a total of 9 raloxifene patients incurred breast cancer. The total number of enrolled placebo patients was 3087, while the total number of enrolled raloxifene patients was 6584.

The following Table II reports some further results from a study utilizing different raloxifene dosage levels.

Table II

Patient No.	Treatment Group	No.of Months
0888	Placebo	22
3601	Placebo	21
2889	Raloxifene 150 mg	20
3857	Raloxifene 30 mg	13
3622	Raloxifene 30 mg	8
5415	Raloxifene 60 mg	13

For all studies pooled, the crude relative risk estimate (RR) of developing breast carcinoma for raloxifene vs. placebo was 0.31(95% confidence interval, 0.13 to 0.71). The probability that these treatment group differences in reported incidence were due to random chance is approximately 0.6%. Approximate incidence rates of cancer reports for each arm for raloxifene and placebo were: Placebo = 4.23, Raloxifene 30 mg = 4.0, Raloxifene 60 mg = 0.6, Raloxifene 120 mg = 1.6, Raloxifene 150 mg = 2.6 (Incidence rates are presented as number of case reports per 1,000 patient-years of exposure to drug).



CLAIMS

1. The use of raloxifene, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament adapted for the administration of from about 30 to about 150 mg per day of said raloxifene, or said pharmaceutically-acceptable salt, to a post-menopausal woman so as to inhibit the development of breast cancer in that woman.

2. The use claimed in Claim 1, wherein the raloxifene is used in the form of its hydrochloride salt.

3. The use claimed in Claim 1 or 2, wherein the raloxifene is used in an amount sufficient to provide from about 60 to about 120 mg per day.

4. The use claimed in Claim 3, wherein raloxifene is used in an amount sufficient to provide about 60 mg per day.