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Docket No.: 62814-A/JPW/GJG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Timothy Norris et al.

Serial No.: 09/711,272 Examiner: T. McKenzie

Filed : November 9, 2000 Group Art Unit: 1624

For : STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6,7-BIS (2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE, METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
June 13, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

AMENDMENT IN RESPONSE TO DECEMBER 13, 2001 OFFICE ACTION AND PETITION FOR A THREE-MONTH EXTENSION OF TIME

This Amendment is submitted in response to the Office Action issued December 13, 2001 by the U.S. Patent and Trademark Office in connection with the above-identified application. A response to the December 13, 2001 Office Action was due March 13, 2002. Applicants hereby request a three-month extension of time from March 13, 2002 to June 13, 2002. The fee for a three-month extension of time is $920.00 and a check including this amount is enclosed. Accordingly, a response to the December 13, 2001 Office Action is now due June 13, 2002 and this Amendment is being timely filed.

Please amend the subject application as follows:

In the Title of the Invention

Please change the title to:

STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6,7-BIS (2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE,

METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

The difference between the new Title and the previously pending Title is shown in the marked-up copy of the Title attached hereto.

In the Claims

Please amend claims 5, 14, 23 and 50 and add new claims 55-72 under the provisions of 37 C.F.R. §1.121(c). The amended set of claims is presented below and the amendments to the claims are indicated in the marked-up set of claims attached hereto.

5. (Amended) A composition comprising a substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier.

14. (Amended) A method of treating abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1.

23. (Amended) A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1 in combination with an anti-tumor agent selected from the group consisting of a mitotic

Sub C6 B3

inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

50. (Amended) A method for prophylaxis against the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms, so as to thereby result in prophylaxis against the development of basal or squamous cell carcinoma of the skin.

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Please add new claims 55-72 as follows:

55. (New) A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91 in a weight % of the B polymorph relative to the A polymorph which is at least 70%.

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56. (New) The composition of claim 55, wherein the B polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

57. (New) The composition of claim 55, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

58. (New) A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim 1 and a pharmaceutically acceptable carrier.

59. (New) The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.

60. (New) The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.

61. (New) A method for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:

a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

b) cooling the solution to between about 65 and 70 °C;

c) clarifying the solution; and

d) precipitating polymorph B by further cooling the clarified solution.

62. (New) A composition comprising a substantially homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range # 1 - Coupled 3.000 to. 40.040 StepSize: 0.040 StepTime 1.00

Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

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