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INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Connell	Richard	D.	East Lyme, CT
Moyer	James	D.	East Lyme, CT
Morin	Michael	J.	Waterford, CT
Kajiji	Shama	M.	Mystic, CT
Miller	Penelope	E.	Mystic, CT
Foster	Barbara	A.	Mystic, CT

TITLE OF THE INVENTION *(280 characters max)*

PHARMACEUTICAL USES FOR N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINES

CORRESPONDENCE ADDRESS

Paul H. Ginsburg
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

ENCLOSED APPLICATION PARTS *(check all that apply)*

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METHOD OF PAYMENT *(check one)*

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Respectfully submitted,

SIGNATURE _____ DATE: March 30, 2000

TYPED or PRINTED NAME Israel Nissenbaum REGISTRATION NO: 27,582 *(if appropriate)*

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PROVISIONAL APPLICATION FILING ONLY

PHARMACEUTICAL USES FOR N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINES

Field of the Invention

The present invention relates to novel uses for N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine and particularly the mesylate, hydrochloride and anhydrous and hydrate forms. These compounds are currently described as being useful in the treatment of hyperproliferative disorders, such as cancers, in mammals.

Background of the Invention

United States Patent No. 5,747,498 issued May 5, 1998, which is incorporated in its entirety herein by reference thereto, refers to [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride as an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders, such as cancers, in humans. The mesylate compounds in the various polymorph forms, described in co-pending application USSN 09/355534, filed April 8, 1999, are of particular use in most administration applications, while the hydrochlorides, further described in co-pending provisional application USSN 60/164907, filed November 11, 1999, are particularly useful in oral administration applications. The disclosures of both applications are fully incorporated herein, by reference thereto.

Summary of the Invention

The present invention relates to the use of the various forms of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine including the mesylate and hydrochloride forms (all polymorph forms) as well as other pharmaceutically acceptable salt forms, and anhydrous and hydrate forms, for treatment, with a therapeutically-effective amount of the aforementioned compounds and a pharmaceutically acceptable carrier, of the specific conditions of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome) and adrenal and skin cancers as well as auto immune and neoplastic cutaneous diseases such as mycoses fungoides, in a mammal, as well as for the chemoprevention of basal or squamous cell carcinomas of the skin, especially in areas exposed to the sun or in persons known to be at high risk for such cancers. In addition, the aforementioned compounds are useful in treatment of atherosclerosis, with epidermal growth factor having been implicated in the hyperproliferation of vascular smooth muscle cells responsible for atherosclerotic plaques (G.E. Peoples et al., Proc. Nat. Acad. Sci. USA 92:6547-6551, 1995).

In addition to direct treatment of the above ailments with the compounds, the utilization and treatment in these and general applications may be as palliative or neo-adjuvant/adjuvant monotherapy, in blocking epidermal growth factor receptors (EGFR) and for use in treatment of

tumors that express a variant form of EGFR known as EGFRvIII as described in the scientific literature (e.g., DK Moscatello et al. Cancer Res. 55:5536-5539, 1995), as well as in a combination with chemotherapy and immunotherapy. Treatment is also possible with both anti-EGFR and anti-EGF antibody combinations or with combination of inhibitors of MMP (matrix-metallo-proteinase), other tyrosine kinases including VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$.(cytotoxic T-lymphocyte antigen 4) and erbB2. Further treatments include MAb to VEGFr, and other cancer-related antibodies including rhuMAb-VEGF (Genentech, Phase III), the erbB2 MAb available as Herceptin (Genentech, Phase III), or the avb3 MAb available as Vitaxin (Applied Molecular Evolution/MedImmune, Phase II).

Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference.

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes). These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors and VEGF receptors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999),

in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference thereto. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), can furthermore be combined with a compound used in the present invention, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference thereto. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with a compound used in the present invention.

Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

The compounds are also useful as radiation sensitizers for cancer treatment and may be combined with anti-hormonal therapies. Parameters of adjuvant radiation therapies are for example contained in PCT/US99/10741, as published on 25 November 1999, in International Publication No. WO 99/60023, the disclosure of which is included herein by reference thereto.

A specific embodiment of the present invention comprises the use of the anhydrous form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate alone or in

the aforementioned combinations or combination treatments. In particular, the anhydrous form includes polymorphs A, B, and C, having X-ray powder diffraction patterns as described in USSN 09/355534.

Another specific embodiment of the present invention comprises N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate monohydrate described in said application.

The hydrochlorides, in polymorphs A and B as described in USSN 60/164907 filed November 11, 1999, with described X-ray diffraction patterns, are particularly suitable for oral use.

Patients who can be treated with N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine including mesylate and hydrochloride forms, according to the methods of this invention include, for example, patients who have been diagnosed as having NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome) and adrenal and skin cancers as well as auto immune and neoplastic cutaneous diseases such as mycoses fungoides, as well as patients with atherosclerosis and for persons known to be high risks for cancers such as basal or squamous cell carcinomas of the skin, especially in areas exposed to the sun, for the chemoprevention thereof.

Detailed Description of the Invention

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate has been found to exist in three distinct anhydrous polymorphic forms A, B and C and also as a monohydrate.

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, exists in two polymorph forms. The various forms may be prepared in any of the ways described in said patent and applications, referred to above.

The *in vitro* activity of the compounds of the present invention in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response, e.g., cancer) may be determined by procedures described in the above referred to and incorporated patent and patent applications.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration. Parenteral administration is usually preferred but for the hydrochloride form, oral administration is preferred.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration and the

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