(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 220 696 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **17.03.93** (51) Int. Cl.5: **A61K 31/505**

(21) Application number: **86114795.7**

(22) Date of filing: **24.10.86**

A request for the addition of Figure 1 has been fild pusuant to Rule 88 EPC.

(54) Use of buspirone for preparing pharmaceutical compositions for alleviation of phobic anxiety.

(30) Priority: **25.10.85 US 791182**

(43) Date of publication of application:
06.05.87 Bulletin 87/19

(45) Publication of the grant of the patent:
17.03.93 Bulletin 93/11

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
DE-A- 2 920 739

J. CLIN. PSYCHIATRY, vol. 44, (8Pt2), August 1983; R.I.ALTESMAN et al., pp. 12-18&NUM;

J. CLIN. PSYCHIATRY, vol. 44, (11sec 2), August 1983; R.I.SHADER et al., pp. 21-29&NUM;

J. PSYCHIAT. RES., vol. 18, no. 1, 1984, Pergamon Press Ltd. (GB); P.TYRER et al., pp. 73-78&NUM;

DISEASE-A-MONTH, vol. 32, no. 7, July 1986, Yearbook Medical Publishers, Inc.; R.R.CROWE et al., pp. 391-444&NUM;

THE AMERICAN JOURNAL OF PSYCHIATRY, vol. 142, no. 7, July 1985, American Psychiatric Association, US; A.BREIER et al., pp. 787-796&NUM;

DSM III, "Anxiety disorders (or Anxiety and Phobic disorders)", American Psychiatric Association, 1980; pp. 235-239&NUM;

(73) Proprietor: **Bristol-Myers Squibb Company**
345 Park Avenue
New York, N.Y. 10154(US)

(72) Inventor: **Kurtz, Neil M.**
129 Cross Highway
Westport, CT 06880(US)
Inventor: **Newton, Roger E.**
1400 Lark Drive
Evansville, IN 47715(US)
Inventor: **Temple, Davis L., Jr.**
1016 Durham Road
Wallingford, CT 06492(US)

(74) Representative: **Kinzebach, Werner, Dr.**
Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49
W-8000 München 86 (DE)

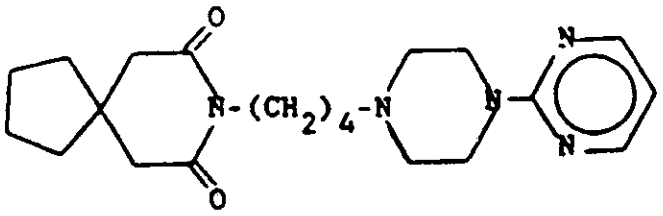
Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

EP 0 220 696 B1

Description

This invention is concerned with the use of the pyrimidine compound 8-[4-(4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione or a pharmaceutically acceptable acid addition salt thereof for preparing pharmaceutical compositions for alleviation of phobic anxiety.

The pyrimidine compound with which the present invention is concerned has the following structural formula



and is known as buspirone. The hydrochloride salt has been referred to in the prior art as MJ 9022-1 and as buspirone hydrochloride. Other acid addition salts thereof are named by combining "buspirone" with the appropriate word to define the acid from which it is prepared as in "buspirone hydrochloride". The latter is the United States Adopted Name (USAN); refer to J. American Med. Assoc. 225, 520 (1973).

The synthesis of the compound and the disclosure. of its psychotropic properties are described in the following patents and publications.

1. Y. H. Wu, et al., J. Med. Chem., 15, 477 (1972).
2. Y. H. Wu, et al., U.S. Patent No. 3,717,634 which issued February 20, 1973.
3. L. E. Allen, et al., Arzneium. Forsch., 24, No. 6, 917-922 (1974).
4. G. L. Sathananthan, et al., Current Therapeutic Research, 18/5, 701-705 (1975).
5. Y. H. Wu, et al., U.S. Patent No. 3,976,776, issued August 24, 1976.

The use of buspirone hydrochloride as a novel anti-anxiety agent for the treatment of neurotic patients is described in G. P. Casten, et al., U.S. Patent No. 4,182,763, issued January 9, 1980. Currently, a New Drug Application (NDA) is pending before the U.S. Food & Drug Administration for the use of buspirone in treatment of anxiety neurosis. In addition, other clinical studies are being conducted to lend support to the use of buspirone for the therapeutic method of the instant invention.

The present invention can be distinguished from the above prior art in that it is directed to a distinct patient population characterized by a disease state different from that related to the anxiolytic process disclosed in the prior art. Support for this distinction is found in the reference, "The Diagnostic Validity of Anxiety Disorders and Their Relationship to Depressive Illness", by A.B. Boyer, Breler et al., in Am. J. Psychiatry, 142:7 (July, 1985), pages 787-796. The diagnosis and treatment of panic disorders has been recently reviewed; cf: D. V. Sheehan, "Panic Attacks and Phobias", New England Journal of Medicine, 307, pages 156-158, 1982; R. I. Shader, et al., "Panic Disorders: Current Perspectives", J. Clin. Pyschopharmacology, 2/6 Supplement, pages 2S-26S, 1982; and W. Matuzas, et al., "Treatment of Agoraphobia and Panic Attacks", Arch. Gen. Psychiatry, 40, pages 220-222, 1983.

J.Psychiatr.Res. 18 (1), 1984, 73-78 is concerned with the short-term drug treatment of anxiety in primary care. Patients were treated with diazepam, buspirone and a placebo in a double-blinded cross-over study. Patients were admitted to the study if their DSM-III primary diagnosis was generalized anxiety disorder, panic disorder or agoraphobia with panic attacks. No essential efficacy differences were detected between the three test substances and it was shown that buspirone gas little different from placebo.

Although panic disorder and in particular phobic anxiety or panic attacks, is a relatively new diagnosis, the basic diagnostic concepts are well known to those skilled in the art and are clearly differentiated from generalized, persistent anxiety. Although the prior art references concerning buspirone disclose the compounds described in the instant application and their tranquilizing and anti-anxiety effects, none of these prior art buspirone references disclose or suggest that these compounds are useful to treat or prevent phobic anxiety which is the applicants' claimed invention.

An example for comparison which distinguishes use in generalized anxiety from use in panic disorder is the drug alprazolam which was disclosed in U.S. Patent No. 3,987,052, issued Cctober, 1976 to Hester as having sedative, tranquilizing and muscle relaxant effects and could be used to alleviate tension and anxiety in mammals. U.S. Patent No. 4,508,726, issued April, 1985, to Coleman discloses and claims the treatment of panic disorders with alprazolam. Further, U.S. Patent No. 4,508,726 admits that alprazolam had been

previously disclosed for the management of anxiety disorders. Alprazolam, a benzodiazepine compound, bears no structural or biochemical relationship to buspirone and would not suggest its usefulness in panic disorders.

In summary, buspirone and its pharmaceutically acceptable salts bear no structural resemblance to any therapeutic agent alleged to be useful in the treatment of panic disorders and in particular phobic anxiety. It is now appreciated by those skilled in the art that generalized anxiety and panic disorders and in particular phobic anxiety are distinguishable disease states with differently defined patient populations. There also exists nothing in the prior art which teaches or suggests that the instant compounds would be useful in alleviation of panic disorder and in particular phobic anxiety.

The use of the present invention is intended for the alleviation of phobic anxiety. The use essentially involves administration of buspirone, or a pharmaceutically acceptable acid addition salt thereof, to one in need of such treatment.

Oral administration of buspirone hydrochloride from 10 to 60 mg per day in divided doses is anticipated as being the preferred dosage regimen.

The treatment of phobic anxiety essentially involves administration of buspirone, or a pharmaceutically acceptable acid addition salt thereof, to a patient in need of such treatment. Pharmaceutically acceptable acid addition salts of buspirone and methods of pharmaceutical formulation are described in the above patents of Wu, et al., U.S. Patent No. 3,717,634 and Casten, et al., U.S. Patent No. 4,182,763.

Administration of buspirone according to the present invention may be made by the parenteral, oral, or rectal routes. The oral route is preferred, however. The clinical dosage range for alleviation of a phobic anxiety is expected to be about the same to slightly higher compared with that for anti-anxiety usage, but can vary to some extent. In general, the expected amount of buspirone administered would be less than 100 mg per day, generally in the 20 mg to 60 mg range, and preferably in the range of 30-60 mg per day. Since the dosage should be tailored to the individual patient, the usual practice is to commence with a dose of 5 mg administered two or three times per day and then to increase the dose every two or three days by 5 mg at each dosage time until the desired response is observed or until the patient exhibits side effects. Single daily dosage may be applicable in some instances.

Claims

1. The use of buspirone or a pharmaceutically acceptable acid addition salt thereof for preparing pharmaceutical compositions for alleviation of phobic anxiety.

2. The use according to claim 1 wherein buspirone hydrochloride is employed for preparing pharmaceutical compositions for oral administration.

Patentansprüche

1. Verwendung von Buspiron oder eines pharmazeutisch verträglichen Säureadditionssalzes davon zur Herstellung pharmazeutischer Mittel zur Linderung von phobischer Angst.

2. Verwendung nach Anspruch 1, wobei Buspiron-Hydrochlorid zur Herstellung pharmazeutischer Mittel zur oralen Verabreichung verwendet wird.

Revendications

1. Utilisation de buspirone ou de son sel d'addition d'acide acceptable en pharmacie pour la préparation de compositions pharmaceutiques pour l'atténuation de l'anxiété phobique.

2. Utilisation selon la revendication 1, où on emploie le chlorhydrate de buspirone pour la préparation de compositions pharmaceutiques pour une administration orale.

REGISTER ENTRY FOR EP0220696

European Application No EP86114795.7 filing date 24.10.1986

Priority claimed:
25.10.1985 in United States of America - doc: 791182

Designated States BE CH DE ES FR GB GR IT LI LU NL SE AT

Title USE OF BUSPIRONE FOR PREPARING PHARMACEUTICAL COMPOSITIONS FOR ALLEVIATION OF PANIC DISORDERS

Applicant/Proprietor
BRISTOL-MYERS COMPANY, 345 Park Avenue, New York New York 10154, United States of America [ADP No. 50481134001]

Inventors
NEIL M. KURTZ, 129 Cross Highway, Westport Connecticut 06880, United States of America [ADP No. 54785696001]

ROGER E. NEWTON, 1400 Lark Drive, Evansville Indiana 47715, United States of America [ADP No. 54785704001]

JR. DAVIS L. TEMPLE, 1016 Durham Road, Wallingford Connecticut 06492, United States of America [ADP No. 54785712001]

Classified to
A5B U1S
A61K

Address for Service
CARPMAELS & RANSFORD, 43 Bloomsbury Square, LONDON, WC1A 2RA, United Kingdom [ADP No. 00000083001]

EPO Representative
DR. WERNER KINZEBACH, Patentanwälte Reitstötter, Kinzebach & Partner Sternwartstrasse 4 Postfach 86 06 49, D-8000 München 86, Federal Republic of Germany [ADP No. 50876911001]

Publication No EP0220696 dated 06.05.1987
Publication in English

Examination requested 24.10.1986

Patent Granted with effect from 17.03.1993 (Section 25(1)) with title USE OF BUSPIRONE FOR PREPARING PHARMACEUTICAL COMPOSITIONS FOR ALLEVIATION OF PHOBIC ANXIETY.

31.01.1989 Notification from EPO of change of EPO Representative details from
DR. WERNER KINZEBACH, Patentanwälte Reitstötter, Kinzebach & Partner Sternwartstrasse 4 Postfach 86 06 49, D-8000 München 86, Federal Republic of Germany [ADP No. 50876911001]
to
DR. WERNER KINZEBACH, Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49, D-8000 München 86, Federal Republic of Germany [ADP No. 50024991001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

04.09.1989 EPO: Search report published on 04.10.1989
Entry Type 25.11 Staff ID. Auth ID. EPT

26.03.1990 Notification from EPO of change of Applicant/Proprietor details from
BRISTOL-MYERS COMPANY, 345 Park Avenue, New York New York 10154, United States of America [ADP No. 50481134001]
to
BRISTOL-MYERS SQUIBB COMPANY (A DELAWARE CORP.), 345 Park Avenue, New York N.Y. 10154, United States of America [ADP No. 57320772001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

15.02.1993 Notification from EPO of change of Applicant/Proprietor details from
BRISTOL-MYERS SQUIBB COMPANY (A DELAWARE CORP.), 345 Park Avenue, New York N.Y. 10154, United States of America [ADP No. 57320772001]
to
BRISTOL-MYERS SQUIBB COMPANY, 345 Park Avenue, New York, N.Y. 10154, United States of America [ADP No. 57320772001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

15.02.1993 Notification from EPO of change of EPO Representative details from
DR. WERNER KINZEBACH, Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49, D-8000 München 86, Federal Republic of Germany [ADP No. 50024991001]
to
DR. WERNER KINZEBACH, Patentanwälte Reitstötter, Kinzebach und Partner Sternwartstrasse 4 Postfach 86 06 49, W-8000 München 86, Federal Republic of Germany [ADP No. 50024991001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

15.02.1993 Notification from EPO of change of Inventor details from
NEIL M. KURTZ, 129 Cross Highway, Westport Connecticut 06880, United States of America [ADP No. 54785696001]

ROGER E. NEWTON, 1400 Lark Drive, Evansville Indiana 47715, United States of America [ADP No. 54785704001]

JR. DAVIS L. TEMPLE, 1016 Durham Road, Wallingford Connecticut 06492, United States of America [ADP No. 54785712001]
to
NEIL M. KURTZ, 129 Cross Highway, Westport, CT 06880, United States of America [ADP No. 60680600001]

ROGER E. NEWTON, 1400 Lark Drive, Evansville, IN 47715, United States of America [ADP No. 60680618001]

JR. DAVIS L. TEMPLE, 1016 Durham Road, Wallingford, CT 06492, United States of America [ADP No. 60680626001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

05.03.1993 CARPMAELS & RANSFORD, 43 Bloomsbury Square, LONDON, WC1A 2RA, United Kingdom [ADP No. 00000083001]
registered as address for service
Entry Type 8.11 Staff ID. SS1 Auth ID. AA

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0220696

PROPRIETOR(S)

Bristol-Myers Squibb Company, 345 Park Avenue, New York, N.Y. 10154, United States of America

DATE FILED 24.10.1986

DATE GRANTED 17.03.1993

DATE NEXT RENEWAL DUE 24.10.1994

DATE NOT IN FORCE

DATE OF LAST RENEWAL 14.10.1993

YEAR OF LAST RENEWAL 08

STATUS PATENT IN FORCE