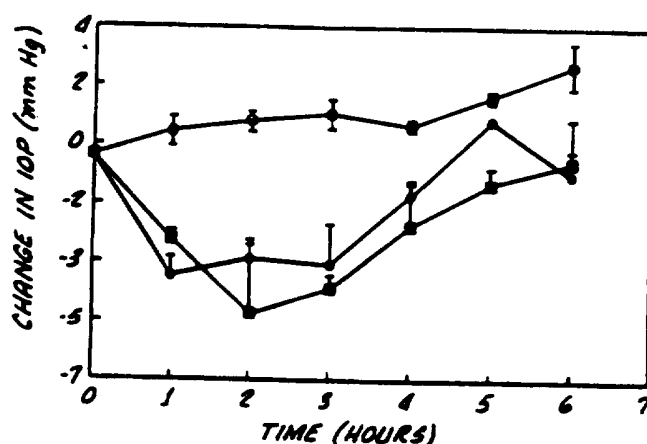




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification <sup>5</sup> :<br>A61K 31/195, 31/42, 31/44<br>A61K 31/445, 31/425, 31/55                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  | A3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | (11) International Publication Number: WO 93/18762<br>(43) International Publication Date: 30 September 1993 (30.09.93) |
| (21) International Application Number: PCT/US93/02402<br>(22) International Filing Date: 16 March 1993 (16.03.93)<br>(30) Priority data:<br>07/856,012                      19 March 1992 (19.03.92)                      US<br>(71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, Post Office Box 19534, Irvine, CA 92713-9534 (US).<br>(72) Inventors: WOLDE MUSSIE, Elizabeth ; 40 Gullwing Avenue, Laguna Niguel, CA 92677 (US). RUIZ, Guadalupe ; 1068 Gentle Drive, Corona, CA 91720 (US).<br>(74) Agents: VOET, Martin, A. et al.; Allergan, Inc., 2525 Dupont Drive, Post Office Box 19534, Irvine, CA 92713-9534 (US). |  | (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).<br><br>Published<br>With international search report.<br>With amended claims.<br><br>(88) Date of publication of the international search report: 28 October 1993 (28.10.93)<br>Date of publication of the amended claims: 25 November 1993 (25.11.93) |                                                                                                                         |

(54) Title: METHOD FOR REDUCING INTRAOCULAR PRESSURE IN THE MAMMALIAN EYE BY ADMINISTRATION OF GAMMA AMINOBUTYRIC ACID (GABA) AGONISTS



## (57) Abstract

Ophthalmic compositions and a method are disclosed for treating glaucoma and/or ocular hypertension in the mammalian eye by topically administering to the mammalian eye the ophthalmic composition of the invention which contains as the active ingredient one or more gamma aminobutyric acid agonist compounds. Examples of gamma aminobutyric acid agonists utilized in the ophthalmic composition and method of treatment are: gamma aminobutyric acid (GABA), 5-(aminomethyl)-3(2H)-isoxazolone (muscimol), 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP) and a pharmaceutically acceptable salt of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol, piperidine-4-sulfonic acid and a pharmaceutically acceptable salt of piperidine-4-sulfonic acid, 3-(2H)-isothiazolone, 5-(aminomethyl) (thiomuscimol), 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam), 7-chloro-1-[2-(diethylamino)ethyl]-5-(fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (flurazepam) and a pharmaceutically acceptable salt of 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide (chlordiazepoxide) and a pharmaceutically acceptable salt of 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide.

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## AMENDED CLAIMS

[received by the International Bureau on 25 October 1993 (25.10.93);  
original claims 1, 2, 5-9, 11, 12 and 14 amended;  
original claims 3, 4, 10, 13, 15, 16 and 18 deleted;  
remaining claims unchanged (4 pages)]

1. An ophthalmic solution useful for reducing intraocular pressure in the eye of a mammal, the solution comprising as its active ingredient one or more gamma aminobutyric acid (GABA) agonist compounds and having the  
5 active ingredient present in the concentration range of 0.1 to 5 percent weight by volume.

2. The ophthalmic solution of Claim 1 where the composition is adapted for administration to the eye of a mammal in the form of eye droplets.

3. Canceled.

10

4. Canceled.

15

5. The ophthalmic solution of Claim 1 where the gamma aminobutyric acid (GABA) agonist is selected from the group consisting of:

gamma aminobutyric acid (GABA),

20 5-(aminomethyl)-3(2H)-isoxazolone (muscimol),

4,5,6,7-tetrahydroisoxazolo[5, 4-c]pyridin-3-ol (THIP) and a pharmaceutically acceptable salt of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol, piperidine-4-sulfonic acid and a pharmaceutically acceptable salt of piperidine-4-sulfonic acid,

25 3-(2H)-isothiazolone, 5-(aminomethyl) (thiomuscimol),

7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam),

7-chloro-1-[2-(diethylamino)ethyl]-5-(2-

fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**flurazepam**) and a pharmaceutically acceptable salt of 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and

7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide  
5 (**chlordiazepoxide**) and a pharmaceutically acceptable salt of 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide.

6. The ophthalmic solution of Claim 5 where the gamma aminobutyric acid agonist is selected from the group consisting of gamma aminobutyric acid (**GABA**) and 5-(aminomethyl)-3(2H)-isoxazolone (**muscimol**).

10 7. The ophthalmic solution of Claim 6 where the gamma aminobutyric acid agonist is gamma aminobutyric acid (**GABA**).

8. The ophthalmic solution of Claim 6 where the gamma aminobutyric acid agonist is 5-(aminomethyl)-3(2H)-isoxazolone (**muscimol**).

9. The ophthalmic solution of Claim 8 adapted for administration to  
15 the eye of a mammal in the form of eye droplets.

10. Canceled.

20

11. A method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal, the method of treatment comprising the steps of administering to the mammal an ophthalmic solution which comprises as its active  
25 ingredient one or more gamma aminobutyric acid agonist compounds and wherein the active ingredient is present in the range of approximately 0.1 to 5 percent weight by volume.

12. The method of treatment of Claim 11 where the solution is adapted for administration to the eye of a mammal in the form of eye droplets.

13. Canceled.

5

14. A method of treating animals of the mammalian species, including humans, for the purpose of reducing intraocular pressure in the eye of the mammal, the method of treatment comprising the steps of administering to the mammal an ophthalmic composition in the form of eye droplets which comprises as its active ingredient one or more gamma aminobutyric acid agonist compounds selected from a group consisting of:

gamma aminobutyric acid (GABA),

15 5-(aminomethyl)-3(2H)-isoxazolone (muscimol),

4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP) and a pharmaceutically acceptable salt of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol, piperidine-4-sulfonic acid and a pharmaceutically acceptable salt of piperidine-4-sulfonic acid,

20 3,4-(2H)-isothiazolone, 5-(aminomethyl) (thiomuscimol),

7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam),

7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (flurazepam) and a pharmaceutically acceptable salt of 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and

7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-

amine 4-oxide (**chlordiazepoxide**) and a pharmaceutically acceptable salt of 7-chloro-N-methyl-5-phenyl-3H-1, 4-benzodiazepin-2-amine 4-oxide, the concentration of the gamma aminobutyric acid agonist in the eye droplets being in the range of the approximately 0.1 to 5 percent weight by volume.

5

15. Canceled.

10

16. Canceled.

17. The method of treatment of Claim 14 where the gamma aminobutyric acid agonist is selected from a group consisting of gamma  
15 aminobutyric acid (GABA), and 5-(aminomethyl)-3(2H)-isoxazolone (**muscimol**).

18. Canceled.

20

19. The method of treatment of Claim 17 wherein the gamma aminobutyric acid agonist is 5-(aminomethyl)-3(2H)-isoxazolone (**muscimol**).

20. The method of treatment of Claim 17 where the gamma aminobutyric acid agonist is gamma aminobutyric acid (GABA).

**STATEMENT UNDER ARTICLE 19(1)**

The presently amended claims call for an ophthalmic solution which contains gamma aminobutyric acid (GABA) agonist compounds as active ingredient for reducing intraocular pressure in the eye of a mammal. Alternatively, the presently amended claims describe a method of reducing intraocular pressure in the eye of a mammal by administering an ophthalmic solution which has a GABA agonist compound as its active ingredient. The presently amended claims do not call for systemic administration of GABA agonist compounds for any purpose.

In contrast with the present invention the cited Andermann, et al. patent reference describes a tissue irrigating solution which is used during eye surgery and which contains gamma aminobutyric acid (GABA) as one of its many ingredients. This patent reference discloses nothing about the ability of GABA and GABA agonists to reduce intraocular pressure.

The reference by Pino Capote in the British Journal of Anaesthesia is substantially in accordance with the general teaching in the prior art, to the effect that if the systemic administration of such a GABA agonist as diazepam

causes a decrease in intraocular pressure at all, such decrease is rather slight and of short duration.

The claims as amended (claims 1, 2, 5-9, 11, 12 and 14) patentably distinguish the present invention over the teaching of the prior art. The canceled claims (claims 3, 4, 10, 13, 15, 16 and 18) remove any redundancies caused by the amendments. All other claims remain unchanged.