



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

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<b>(21) International Application Number:</b> PCT/EP98/01920  <b>(22) International Filing Date:</b> 25 March 1998 (25.03.98)  <b>(30) Priority Data:</b> 97200881.7 27 March 1997 (27.03.97) EP (34) Countries for which the regional or international application was filed: NL et al. 97202785.8 11 September 1997 (11.09.97) EP (34) Countries for which the regional or international application was filed: NL et al.  <b>(71) Applicant (for all designated States except US):</b> AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BROEKKAMP, Christophorus, Louis, Eduard [NL/NL]; Vorstengraflaan 1, NL-5342 LM Oss (NL). BERENDSEN, Hermanus, Henricus, Gerardus [NL/NL]; Heegterstraat 9, NL-5836 CN Geffen (NL). PINDER, Roger, Martin [GB/NL]; Cesar Francklaan 17, NL-5343 EV Oss (NL).  <b>(74) Agent:</b> KRAAK, H.; P.O. Box 20, NL-5340 BH Oss (NL).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> NEW THERAPEUTIC COMBINATIONS OF MIRTAZAPINE AND ANTIPSYCHOTIC AGENTS, FOR THE TREATMENT OR PROPHYLAXIS OF PSYCHOTIC DISORDERS		
<b>(57) Abstract</b>  The present invention relates to therapeutic combinations of mirtazapine and an antipsychotic agent, to pharmaceutical compositions containing said combinations and to their use in the treatment or prophylaxis of psychotic disorders.		

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## NEW THERAPEUTIC COMBINATIONS OF MIRTAZAPINE AND ANTIPSYCHOTIC AGENTS, FOR THE TREATMENT OR PROPHYLAXIS OF PSYCHOTIC DISORDERS

The present invention relates to therapeutic combinations of mirtazapine and an antipsychotic agent, to pharmaceutical compositions containing said combinations and to their use in the treatment or prophylaxis of psychotic disorders.

The term antipsychotic agent includes those classical antipsychotics which work via dopamine D<sub>2</sub> receptor blockade and which are often referred to as "typical" antipsychotics or neuroleptics, and those new antipsychotics which are referred to as "atypical" antipsychotic agents. This atypicality has been defined in a number of ways, but recently it has been defined as the property of providing equal efficacy to established antipsychotic agents while producing fewer extrapyramidal side effects (Meltzer H.Y. Br. J. Psychiatry, 1996, 168 Suppl. 129:23-31). Examples of such typical and atypical antipsychotics include acepromazine, chlorproethazine, chlorpromazine, cyamemazine, fluopromazine, methotrimeprazine, promazine, mesoridazine, pericyazine, piperacetazine, pipothiazine, sulforidazine, thioridazine, acetophenazine, carphenazine, dixyrazine, fluphenazine, perazine, perphenazine, prochlorperazine, thiopropazate, thioproperazine, trifluoperazine, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, benperidol, bromperidol, droperidol, fluanisone, haloperidol, melperone, moperone, pipamperone, spiperone, timiperone, trifluoperidol, fluspirilene, penfluridol, pimozide, amisulpride, raclopride, remoxipride, sulpiride, sultopride, tiapride, molindone, oxypertine, clozapine, loxapine, risperidone, olanzapine, sertindole, quetiapine and ziprasidone.

It has now been found that the administration of mirtazapine, which is one of the newest antidepressant agents and has been disclosed in US patent No. 4,062,848, in combination with an antipsychotic agent is able to enhance the antipsychotic effect of said antipsychotic.

It is a feature of this invention that the use of such drug combinations will enhance the effect of the antipsychotic agent to be used and therefore allow reduced quantities

of an antipsychotic agent to be used and furthermore, therefore allow better management of drug related toxicity and side effects.

Thus according to one aspect, the present invention provides a combination  
5 comprising mirtazapine and an antipsychotic agent as herein before described. Preferably the combination includes mirtazapine.

It will be understood that the present invention also includes derivatives of mirtazapine and the antipsychotic agents. Such derivatives include the  
10 pharmaceutically acceptable salts thereof. Suitable salts include acid addition salts, for example, hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation.

Combinations of mirtazapine and an antipsychotic agent may hereinafter be  
15 referred to as combinations according to the invention.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulation or sequentially. If there is sequential administration, the delay in administering the second  
20 active ingredient should not be such as to lose the benefit of the efficacious effect of the combination of the active ingredients.

The present invention further provides combinations according to the invention for use in therapy, more particularly in the treatment or prophylaxis of psychotic disorders  
25 such as schizophrenia, mania, hyperactivity, substance abuse, emesis and schizophreniaform disorders.

The present invention further includes a method for the treatment of an animal, for example, a mammal including a human, suffering from or liable to suffer from a  
30 psychotic disorder, including any of the aforementioned disorders, which comprises administering an effective amount of a combination according to the invention.

A further feature of the present invention is the method of reducing the amount of antipsychotic agent required to produce an antipsychotic effect in an animal which comprises treating said animal with a therapeutically effective amount of a combination according to the present invention.

5

The present invention also provides the use of mirtazapine in the manufacture of a medicament for administration simultaneously or sequentially with an antipsychotic agent for the treatment and/or prophylaxis of a psychotic disorder. It will be appreciated that an antipsychotic agent may be used in the manufacture of the above medicament for administration simultaneously or sequentially with mirtazapine.

10

Administration of an antipsychotic agent in combination with mirtazapine allows a lower dosing of the antipsychotic agent to achieve the same antipsychotic effect. The dosage of the antipsychotic agent may be reduced by 25-90%, for example, 40-80% and typically 50-70%.

15

The reduction in the amount of antipsychotic agent required will be dependent on the amount of mirtazapine given. Typically the dose of mirtazapine used is that described *infra*.

20

The amount of a combination of mirtazapine and an antipsychotic agent required to produce the efficacious effect will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

25

In general, a suitable dose of mirtazapine for administration to a human will be in the range of 0.01 to 30 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 5 mg per kilogram body weight per day and most preferably in the range of 0.3 to 1.0 mg per kilogram body weight per day.

30

A suitable dose of an antipsychotic agent will be in the range of 0.001 to 25 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 10 mg per kilogram body weight per day and most preferably in the range 0.25 to 5 mg per kilogram body weight per day.

5

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

10 While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable  
15 carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical formulation.

20 A combination of mirtazapine and an antipsychotic agent may conveniently be presented as a pharmaceutical formulation in a unitary dosage form. A convenient unitary dosage formulation contains the active ingredients in amounts of from 0.1 mg to 1 g each for example, 5 mg to 100 mg. Typically unit dosages may, for example, contain 5 to 50 mg, preferably 10 mg of mirtazapine.

25

More commonly these days pharmaceutical formulations are prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patients supply of a pharmaceutical from a bulk supply, in  
30 that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physicians instructions.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, with a package insert directing the patient to the correct use of the invention is a desirable additional  
5 feature of this invention. Suitable dosage units of mirtazapine are for instance, 5 to 50 mg and suitable dosage units containing an antipsychotic agent are 0.1 to 100 mg.

According to a further aspect of the invention, there is provided a patient pack comprising at least one active ingredient of the combination of the invention and an  
10 information insert containing directions on the use of the combination of the invention.

According to another aspect the invention provides a double pack comprising in association for separate administration either mirtazapine and an antipsychotic agent.

15 Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al., Remington's Pharmaceutical  
20 Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and their Manufacture). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring  
25 agents and wetting agents.

Formulations suitable for oral administration may be presented as discrete units such as pills, tablets or capsules each containing a predetermined amount of active ingredient; as a powder or granules; as a solution or suspension. The active ingredient  
30 may also be present as a bolus or paste, or may be contained within liposomes.

Formulations for rectal administration may be presented as a suppository or enema.

For parenteral administration, suitable formulations include aqueous and non-aqueous sterile injection. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Formulations suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurised aerosols, nebulisers or insufflators.

The compounds of the combination of the present invention may be obtained in a conventional manner. Mirtazapine may be prepared using the methods described in US 4,062,843.

The antipsychotic agents may be prepared by methods known in the chemical literature. Haloperidol may, for example, be synthesized using the methods described in US patent no. 3,438,991.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

The interaction of mirtazapine with the neuroleptic compound haloperidol was evaluated in the apomorphine climbing test. It was found that the effect of haloperidol on apomorphine-induced climbing behaviour was enhanced by mirtazapine.

Administration of the dopamine agonist apomorphine induces in mice a peculiar motor behaviour consisting mainly in rearing or climbing vertical up the walls of the cage. This behaviour is elicited by stimulation of dopamine receptors in the striatum because it is suppressed after coagulation of this structure and facilitated when the



receptors in this area are made hypersensitive by pretreatments with 6-hydroxydopamine or haloperidol. Lesions of the nucleus accumbens did not change the climbing behaviour. This climbing behaviour induced by apomorphine is antagonised by antipsychotics including clozapine and sulpiride (Protais et al 1976; Costentin et al, 1975, Von Voigtlander et al 1975; Puech et al, 1978; Costall et al 1978).

It is now reported how the inhibition of apomorphine-induced climbing behaviour by haloperidol is influenced by concomitant treatment with the new antidepressant mirtazapine.

### Materials and methods

The test method used is described in Protais et al 1976, Climbing behaviour induced by apomorphine in mice : a simple test for the study of dopamine receptors in striatum. Psychopharmacology 50: 1-6. Male mice (CrL:CD-1(lcR)BR from Charles River, Germany or MFI from Harlan OLAC UK) weighing 21-25 g were used. Groups of 10 mice each were subcutaneously (s.c.) injected with placebo or mirtazapine and a dose of haloperidol or risperidone at the same time. Thirty minutes later all mice were s.c. injected with apomorphine 1 mg/kg or 0.75 mg/kg. Immediately after the apomorphine injection they were placed individually in a wire mesh cylinder (diameter 12 cm, height 14 cm). At 10 and 20 min hereafter the climbing behaviour of the mice is scored as follows: 4 paws on the floor = 0; 1 or 2 paws holding the wall = 1; 3 or 4 paws holding the wall = 2. For each mouse the total score of the observations at 10 and 20 min is calculated and the mean score for each treatment group is determined. The mean score of the control group should be at least 2.0 (maximum possible score is 4.0). An indication of significance is tested with the 2-tailed Yates test.

### Results and discussion

The results for the haloperidol experiment are shown in Fig 1/2. The mean score of the placebo group  $\pm$  standard error of the mean (S.E.M.) was  $3.35 \pm 0.20$ . The mean scores  $\pm$  S.E.M. after haloperidol 22 and 46  $\mu\text{g/kg}$  were  $3.2 \pm 0.33$  and  $2.6 \pm 0.37$

respectively. The inhibition of climbing behaviour by haloperidol was dose dependently enhanced if the mice were concomitantly treated with mirtazapine (1 and 10 mg/kg). Results of an experiment with mirtazapine only demonstrated that mirtazapine up to 22 mg/kg had no effect on apomorphine climbing behaviour; see Figure 2/2

5

Results for experiments with risperidone and quetiapine are presented in Tables 1 and 2.

Table 1 The figures represent the % inhibition in apomorphine climbing.

Dose of Risperidone (mg/kg)	A	B	C
	Risp	Risp + 1 mg Mirt.	Risp + 10 mg Mirt
0.000	0.0	0.0	0.0
0.010	-30.2	-52.0	-68.8
0.022	-55.3	-64.0	-71.9
0.046	-68.2	-80.0	-100.0
0.100	-88.9	-96.0	-100.0

10

Quetiapine (mg.kg <sup>-1</sup> )	A	B
	Quet	Quet. + 1mg Mirt.
0.0	0.0	0.0
1.0		-41.4
2.2	-35.3	-82.8
4.6	-67.7	-100.0
10.0	-97.1	-100.0
22.0	-100.0	

## LEGEND TO THE FIGURES

## Fig 1/2

- 5        Effect of mirtazapine on apomorphine ( 1 mg/kg)-induced climbing behaviour in mice. Mirtazapine was injected s.c 30 min before apomorphine. \*P <0.05 if compared to placebo treatment.

## Fig 2/2

- 10       Effect of haloperidol and of haloperidol + mirtazapine treatment on apomorphine (1 mg/kg)-induced climbing behaviour in mice.

\*P<0.05; \*\*P<0.01; \*\*\*P<0.001 if compared to placebo + placebo treated group.  
°P<0.05; °°P<0.01 if compared to placebo + haloperidol treated group.

## CLAIMS

1. A combination comprising mirtazapine and an antipsychotic agent.
- 5 2. A combination according to claim 1 wherein the antipsychotic agent is a typical or atypical antipsychotic agent.
3. A combination according to claim 1 wherein the antipsychotic agent is selected  
10 from acepromazine, chlorproethazine, chlorpromazine, cyamemazine, fluopromazine, methotrimeprazine, promazine, mesoridazine, pericyazine, piperacetazine, pipothiazine, sulforidazine, thioridazine, acetophenazine, carphenazine, dixyrazine, fluphenazine, perazine, perphenazine, prochlorperazine thiopropazate, thioproperazine, trifluperazine, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, benperidol, bromperidol, droperidol,  
15 fluanisone, haloperidol, melperone, moperone, pipamperone, spiperone, timiperone, trifluperidol, fluspirilene, penfluridol, pimozide, amisulpride, raclopride, remoxipride, sulpiride, sultopride, tiapride, molindone, oxypertine, clozapine, loxapine, risperidone, olanzapine, sertindole, quetiapine and ziprasidone.
- 20 4. A combination according to claim 1 wherein the antipsychotic agent is selected from acepromazine, chlorpromethazine, chlorpromazine, cyamemazine, fluopromazine, methotrimeprazine, promazine, mesoridazine, pericyazine, piperacetazine, pipothiazine, sulforidazine, thioridazine, acetophenazine,  
25 carphenazine, dixyrazine, fluphenazine, perazine, perphenazine, prochlorperazine thiopropazate, thioproperazine, trifluperazine, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, benperidol, bromperidol, droperidol, fluanisone, haloperidol, melperone, moperone, pipamperone, spiperone, timiperone, trifluperidol, fluspirilene, penfluridol,  
30 pimozide, amisulpride, raclopride, remoxipride, sulpiride, sultopride, tiapride, molindone, oxypertine, clozapine, loxapine, risperidone and olanzapine.
5. A combination according to any of claims 1 to 4 for use in medical therapy.
- 35 6. A pharmaceutical formulation comprising a combination according to any of claims 1 to 4 in association with one or more pharmaceutically acceptable carriers therefor.

- 5 7. A method for the treatment of a psychotic disorder in an animal which comprises treating said animal with a therapeutically effective amount of a combination as defined in any of claims 1 to 4 or a formulation described in claim 6.
- 10 8. Use of mirtazapine in the manufacture of a medicament for administration either simultaneously or sequentially with an antipsychotic agent for the treatment and/or prophylaxis of a psychotic disorder.
9. Use of an antipsychotic agent in the manufacture of a medicament for administration either simultaneously or sequentially with mirtazapine for the treatment and/or prophylaxis of a psychotic disorder.
- 15 10. Use of mirtazapine and an antipsychotic agent in the manufacture of a medicament for the treatment and/or prophylaxis of a psychotic disorder.
- 20 11. A patient pack comprising at least one active ingredient selected from mirtazapine and an antipsychotic agent, and comprising an information insert containing directions on the use of the active ingredient, or the active ingredients, in a combination comprising mirtazapine and an antipsychotic agent.

Figure 1

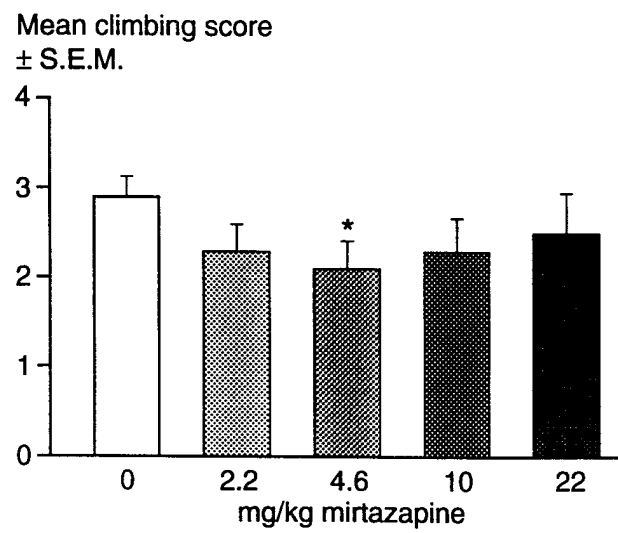
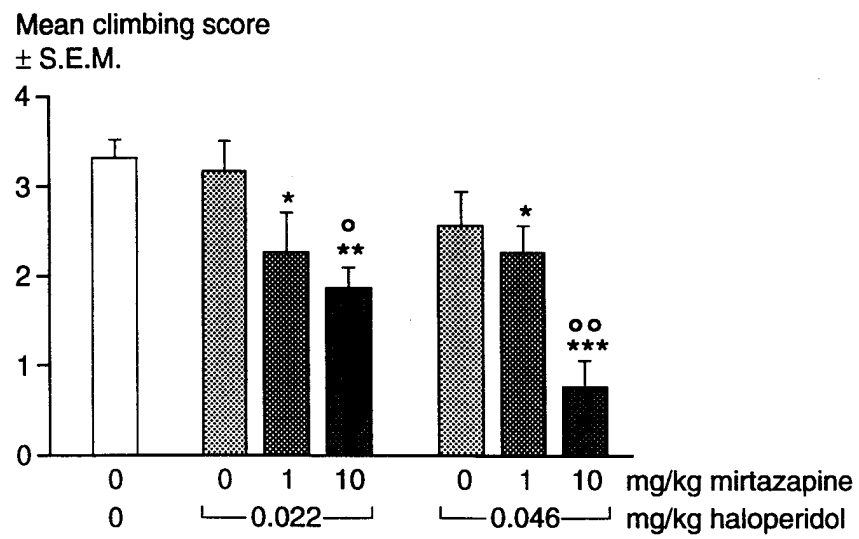


Figure 2



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/01920

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/55

According to International Patent Classification(IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BERENDSEN ET AL: "Mirtazapine Enhances the Effect of Haloperidol on Apomorphine-Induced Climbing Behavior in Mice and Attenuates Haloperidol-Induced Catalepsy in Rats" PSYCHOPHARMACOLOGY, vol. 135, no. 3, 1998, pages 284-289, XP002073590 see page 284, left-hand column see page 285, left-hand column, paragraph 1  --- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/01920

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GOWER ET AL: "Pharmacological Evaluation of in vivo tests for alpha-2 Adrenoceptor Blockade in the CNS and the Effects of the Enantiomers of Mianserin and its Aza-Analog ORG3770" ARCH .INT. PHARMACODYN. THER., vol. 291, 1988, pages 185-201, XP002073591 see page 186 see page 194; table 7 see page 199 ---	1-11
Y	NEAL-BELIVEAU ET AL: "SEROTONERGIC INVOLVEMENT IN HALOPERIDOL-INDUCED CATALEPSY" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 265, no. 1, 1993, pages 204-217, XP002034772	1-11
A	see page 207 see page 209, left-hand column, paragraph 5 see page 214, left-hand column, line 3-10 ---	4,5
A	WO 94 02138 A (IVY MARY ELIZABETH) 3 February 1994 see page 4, line 25-26 see page 5, line 2-4 ---	1-11
A	BIOLOGICAL ABSTRACTS, vol. 84, Philadelphia, PA, US; abstract no. 101722, XP002034774 see abstract & OHSUKA ET AL: "5-HT <sub>2</sub> receptorsensitivity in chronic schizophrenics during the combination therapy of pimozide and mianserin" NEUROSCIENCES, vol. 13, no. 2, 1987, pages 223-225, KOBE ---	1-11
A	BARBHAIYA ET AL: "INVESTIGATION OF PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS AFTER COADMINISTRATION OF NEFAZODONE AND HALOPERIDOL" JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, vol. 16, no. 1, February 1996, pages 26-34, XP002034771 see page 27, right-hand column, line 4-14, paragraph 1; figure 1; table 2 see page 30, left-hand column, line 2-18, paragraph 1-2 see page 33, left-hand column, line 3-8 --- -/--	1-11

# INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PATENT ABSTRACTS OF JAPAN vol. 096, no. 001, 31 January 1996 &amp; JP 07 242669 A (AKIKAZU OGAWA), 19 September 1995 see abstract</p> <p style="text-align: center;">---</p>	1-11
A	<p>DE 24 10 821 A (HOECHST AG) 18 September 1975 see page 2, paragraph 6 see page 3, paragraph 3 see page 3, paragraph 5 see page 4, paragraph 1</p> <p style="text-align: center;">---</p>	1-11
A	<p>BALANT-GORGIA ET AL: "THERAPEUTIC DRUG MONITORING AND DRUG-DRUG INTERACTIONS: A PHARMACOEPIDEMOLOGICAL PERSPECTIVE" THÉRAPIE, vol. 51, no. 4, 1996, pages 399-402, XP002034773 see page 400, left-hand column, paragraph 2-3; table 1 see page 288, left-hand column, paragraph 2 see page 285, left-hand column, paragraph 3-4</p> <p style="text-align: center;">-----</p>	1-11

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/ 01920

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 7-11  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/01920

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9402138 A	03-02-1994	AU 4674693 A	14-02-1994
		EP 0651638 A	10-05-1995
		ZA 9305078 A	07-02-1994
DE 2410821 A	18-09-1975	FR 2262997 A	03-10-1975