# A NEW COMPOSITION

## Field of the Invention

The present invention relates to a composition which comprises a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is paroxetine, or a pharmaceutically acceptable salt and/or solvate thereof. The present invention also relates to a process for the preparation of the inventive composition, pharmaceutical formulations containing said composition and to the use of said composition either by concomitant administration or by separate administration as an improvement of the treatment of affective disorders such as depression, anxiety, obsessive compulsive disorder (OCD), etc.

## Background of the Invention

Today, it is generally considered that antidepressants take 2-4 weeks to reach full clinical effect. In contrast, the side effects occur immediately. Thus, slow onset of action of antidepressants leads to a vulnerable period for patients in which they experience the side effects, but not the therapeutic effects of drugs. There is often a heavy burden on the treating physician to persuade the patient to continue with the treatment during this period. Furthermore, in suicidal patients, as the onset of action is gradual, initiative may be regained without the experiencing of full reversal of symptoms, leaving a window of risk for suicide and a frequent requirement for hospitalization. An antidepressant with fast onset of action would not only be beneficial due to the faster symptom reduction, but would also be more acceptable to patients and physicians and reduce the need for and duration of hospitalization. The same long period to reach full clinical effect has been shown in the treatment of other affective disorders such as anxiety and OCD.

## Prior art

In WO 96/33710 is disclosed that the compound *(R)*-5-carbamoyl-8-fluoro-3-*N,N*-dicyclobutylamino-3,4-dihydro-2*H*-1-benzopyran which has high affinity to 5-HT receptors and antagonizes 5-$HT_{1A}$ mediated responses induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors.

## Summary of the Invention

The present invention is directed to a new composition comprising of a first component (a) which is the specific 5-$HT_{1A}$antagonist *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is paroxetine, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof. Said composition attains a faster onset of action and consequently, provides a more efficacious treatment of the patients suffering form affective disorders, particularly depression.

It has been shown in animal studies that acute administration of selective 5-HT reuptake inhibitors (SSRIs) decreases the electrical impulse propagation in 5-HT neurones via a negative feedback reaction probably mediated by collateral 5-HT axons releasing 5-HT in raphé nuclei. By inhibiting the somatodendritic 5-$HT_{1A}$ autoreceptors in the raphé nuclei the selective antagonists counteract the decrease in propagetion caused by 5-HT reuptake inhibitors. This indicates that a selective blockade of somatodendritic autoreceptor i.e. 5-$HT_{1A}$ antagonist may have a clinical potential to improve the efficacy of 5-HT reuptake inhibitors (SSRIs) and offer a new rationale for rapid onset of effect in the treatment of affective disorders, for instance the antidepressant actions.

The compound *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299) disclosed herein is

described in J. Pharmacol. Exp. Ther., 283, 216-225, (1997) as a selective 5-$HT_{1A}$ receptor antagonist.

*(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate possesses a high affinity to the specific subgroup of 5-$HT_{1A}$ receptor in the CNS and acts as an antagonist on that 5-$HT_{1A}$ receptor, and also shows favourable bioavailability after oral administration.

Paroxetine is a 5-HT reuptake inhibitor (SSRI) which is commercially available. Pharmaceutically acceptable salts of paroxetine such as the hydrochloride, hydrobromide, maleate, tartrate, acetate etc. are also included in the inventive composition. Also solvate forms such as the hydrate and hemihydrate of the salts are included.

The composition according to the present invention may exist in one pharmaceutical formulation comprising the component (a) and component (b), or in two different pharmaceutical formulations, one for component (a) and one for component (b). The pharmaceutical formulation may be in the form of tablets or capsules, powders, mixtures, solutions or other suitable pharmaceutical formulation forms such as patches and nasal formulations.

The composition of the present invention can be prepared such that component (a) is incorporated into the same pharmaceutical formulation as component (b) by e.g. mixing in a conventional way.

The present invention also includes a method of improving the onset of therapeutic action by concomitant administration of a composition comprising of *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and paroxetine.

A further embodiment of the present invention is a kit containing a dosage unit of *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of a paroxetine, optionally with instructions for use.

**Pharmaceutical formulations**

According to the present invention the compounds in the composition will normally be administered orally, rectally, transdermally, nasally or by injection, in the form of pharmaceutical formulations comprising the active ingredients in a pharmaceutically acceptable dosage form . The dosage form may be a solid, semisolid or liquid formulation. Usually the active substances will constitute between 0.1 and 99% by weight of the formulation, more specifically between 0.5 and 20% by weight for formulations intended for injection and between 0.2 and 50% by weight for formulations suitable for oral administration.

The pharmaceutical formulation comprises the active ingredients, optionally in association with adjuvants, excipients e.g. diluents, and/or inert carriers.

To produce pharmaceutical formulations of the composition of the invention in the form of dosage units for oral application, the selected compounds may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatin or poly-vinylpyrrolidone, disintegrants e.g. sodium starch glycolate, cross-linked PVP and cross-caramellose sodium and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and an antisticking agent such as talc or colloidal silicon dioxide, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a polymer known to the man skilled in the art e.g. HPMC, HC or other cellulose derivatives or PVP, wherein the polymer is dissolved in water or a readily volatile organic solvent or mixture of organic

solvents. Alternatively, the tablets can be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatin, talcum, titanium dioxide, and the like. Dyestuffs may be added to these coatings for instance in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the formulation of soft gelatin capsules, the active substances may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatin capsules may contain granules of the active substances using any of the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives, plasticizers, polyetheneglycol, waxes, lipids or gelatin. Also liquids or semisolids of the drug can be filled into hard gelatin capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substances in a mixture with a neutral fatty base, or gelatine rectal capsules comprising the active substances in admixture with vegetable oil or paraffin oil. Liquid formulations for oral application may be in the form of solutions, syrups or suspensions, for example solutions containing from about 0.2% to about 20% by weight of the active substances herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid formulations may contain colouring agents, flavouring agents, saccharin and carboxymethyl-cellulose as a thickening agent or other excipients known to a person skilled in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substances, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the active compounds in the composition of the invention in therapeutic treatment of humans are about 0.01-100 mg/kg bodyweight for peroral administration and 0.001-100 mg/kg bodyweight for parenteral administration. The daily doses of the active ingredient *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate may very well differ from the daily doses of the active ingredient paroxetine but the doses can also be the same for both of the active ingredients.

**Medical and Pharmaceutical Use**

In a further aspect the present invention provides the use of the composition comprising a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is paroxetine, in the treatment of 5-hydroxytryptamine mediated disorders, such as affective disorders. Examples of affective disorders are disorders in the CNS such as mood disorders (depression, major depressive episodes, dysthymia, seasonal affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders (disorders of impulse control, trichotellomania) and sleep disorders. Other disorders in the CNS such as eating disorders (obesity, anorexia, bulimia), premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders (age associated memory impairment, presenile and senile dementia such as Alzheimer's disease), pathological aggression, schizophrenia, endocrine disorders (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain and hypertension may also be treated with the combination described herein. Examples of other hydroxytryptamine mediated disorders are urinary incontinence, vasospasm and growth control of tumors (e g lung carcinoma) and it may be possible to treat those with the combination described herein as well.

**Pharmacology**

**Antagonism by *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299) of the paroxetine induced suppression of dorsal raphe firing.**

Materials and methods

Adult male Sprague Dawley rats (B&K Universal, Sollentuna, Sweden) were used and were housed under controlled climate conditions. The animals were prepared for electrophysiological recordings according to standard procedures. Briefly, the rats were deeply anaesthetized with chloral hydrate and mounted in a stereotaxic frame. Extracellular recording electrodes were lowered into the dorsal raphe, guided by stereotaxic co-ordinates, and target neurones were identified by the firing characteristics of serotonin neurones in this nucelus. The animals were kept anaesthetized throughout the experiments and drugs were administered intravenously through a tail vein catheter. Paroxetine (0.1 mg $kg^{-1}$ i.v.) was administered 3 min before NAD 299 (50 nmol $kg^{-1}$ i.v.)

Results

It was also found that NAD 299 could antagonize the suppression of firing in serotoninergic dorsal raphe neurones in rats induced by paroxetine (Figure). The figure shows medians $\pm$semi-interquartile range based on recordings from 5 animals per group. Statistical evaluation for differences between treatment groups and controls, performed by means of the Mann-Whitney $\mu$-test, is also shown in the figure. In addition, the paroxetine-induced suppression was statistically significantly antagonised by NAD 299 treatment ($p<0.05$).

Discussion and conclusions

It is generally considered that selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, owe their antidepressant efficacy to their ability to enhance the synaptic availability of serotonin in forebrain target areas of serotoninergic projections from the

midbrain raphe nuclei. However, the 5-hydroxytryptamine (5-HT) transporter protein affected is present both in somatodendritic and terminal regions, and initially the enhanced availability of serotonin in the former areas will inhibit neuronal activity as well as forebrain synthesis and release of 5-HT through activation of inhibitory $5\text{-HT}_{1A}$ autoreceptors. As these receptors desensitize with time there is a gradual increase in forebrain serotonin release, as has been shown in animals studies, and the time-course for this phenomenon probably explains the delayed onset of antidepressant actions clinically.

There exists the hypothesis that disinhibition of the self-inhibitory effects of SSRIs by blockade of inhibitory $5\text{-HT}_{1A}$ autoreceptors should produce a faster onset of action, and also generally increase the efficacy of these agents.

The data show that *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299) effectively antagonizes the inhibition of firing in serotoninergic neurones produced by acute administration of paroxetine in the rat.

The following non-limiting Example serves to illustrate the present invention.

**Example**

A suitable pharmaceutical composition comprising a first component (a) and a second component (b) in a single dosage form include the following:

| Composition | mg/tablet |
|---|---|
| Active drug component (a) | 5 |
| Active drug component (b) | 20 |
| Microcrystalline cellulose | 100 |
| Corn starch | 40 |
| Povidone | 4 |
| Water | 50 |
| Sodium starch glycolate | 8 |
| Magnesium stearate | 1 |

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## CLAIMS

1. A composition comprising of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is paroxetine in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof.

2. Use of the composition according to claim 1 for the manufacture of a medicament for the treatment of 5-HT mediated disorders.

3. The use according to claim 2 for the manufacture of a medicament for the treatment of affective disorders.

4. The use according to claim 3 for the manufacture of a medicament for the treatment of mood disorders.

5. The use according to claim 4 for the manufacture of a medicament for the treatment of depression.

6. A method for the treatment of 5-HT mediated disorders by administering to a patient suffering therefrom the composition defined in claim 1.

7. The method according to claim 6 for the treatment of affective disorders.

8. The method according to claim 6 for the treatment of mood disorders.

9. The method according to claim 8 for the treatment of depression.

10. A method of improving the onset of therapeutic action by concomitant administration of a composition defined in claim 1.

11. A pharmaceutical formulation wherein the active ingredients are those in the composition defined in claim 1, optionally in association with adjuvants, excipients and/or inert carriers.

12. A pharmaceutical formulation according to claim 11 wherein the first component (a) is concomitantly administered with the second component (b).

13. A pharmaceutical formulation according to any one of claims 11-12 for use in the treatment of 5-HT mediated disorders.

14. A pharmaceutical formulation according to any one of claims 11-12 for use in the treatment of affective disorders.

15. A pharmaceutical formulation according to any one of claims 11-12 for use in the treatment of mood disorders.

16. A pharmaceutical formulation according to any one of claims 11-12 for use in the treatment of depression.

17. A process for the preparation of the composition according to claim 1 whereby the first component (a) is incorporated into the same pharmaceutical formulation as the second component (b).

18. A process for the preparation of the composition according to claim 1 whereby the first component (a) is in a one pharmaceutical formulation and is combined with the second component (b) is in a different pharmaceutical formulation.

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19. A kit containing a dosage unit of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of a second component (b) which is paroxetine, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, optionally with instructions for use.

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## AMENDED CLAIMS

[received by the International Bureau on 15 February 2000 (15.02.00);
original claims 6,11 and 19 amended; remaining claims unchanged (3 pages)]

1. A composition comprising of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is paroxetine in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof.

2. Use of the composition according to claim 1 for the manufacture of a medicament for the treatment of 5-HT mediated disorders.

3. The use according to claim 2 for the manufacture of a medicament for the treatment of affective disorders.

4. The use according to claim 3 for the manufacture of a medicament for the treatment of mood disorders.

5. The use according to claim 4 for the manufacture of a medicament for the treatment of depression.

6. The use according to claim 2 in the manufacture of a medicament in the prevention or in the treatment of urinary incontinence.

7. A method for the treatment of 5-HT mediated disorders by administering to a patient suffering therefrom the composition defined in claim 1.

8. The method according to claim 7 for the treatment of affective disorders.

9. The method according to claim 7 for the treatment of mood disorders.

10. The method according to claim 9 for the treatment of depression.

11. A method according to claim 7 for the prevention or the treatment of urinary incontinence.

12. A method of improving the onset of therapeutic action by concomitant administration of a composition defined in claim 1.

13. A pharmaceutical formulation wherein the active ingredients are those in the composition defined in claim 1, optionally in association with adjuvants, excipients and/or inert carriers.

14. A pharmaceutical formulation according to claim 13 wherein the first component (a) is concomitantly administered with the second component (b).

15. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of 5-HT mediated disorders.

16. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of affective disorders.

17. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of mood disorders.

18. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of depression.

19. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of urinary incontinence.

20. A process for the preparation of the composition according to claim 1 whereby the first component (a) is incorporated into the same pharmaceutical formulation as the second component (b).

21. A process for the preparation of the composition according to claim 1 whereby the first component (a) is in a one pharmaceutical formulation and is combined with the second component (b) is in a different pharmaceutical formulation.

22. A kit containing a dosage unit of a first component (a) which is *(R)*-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of a second component (b) which is paroxetine, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, optionally with instructions for use.