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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/535 — A1

(11) International Publication Number: **WO 99/64006**

(43) International Publication Date: 16 December 1999 (16.12.99)

(21) International Application Number: PCT/GB99/01797

(22) International Filing Date: 8 June 1999 (08.06.99)

(30) Priority Data:

| | | |
|---|---|---|
| 9812620.4 | 11 June 1998 (11.06.98) | GB |
| 9812618.8 | 11 June 1998 (11.06.98) | GB |
| 9812616.2 | 11 June 1998 (11.06.98) | GB |
| 9812666.7 | 11 June 1998 (11.06.98) | GB |

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: USE OF A NK–1 RECEPTOR ANTAGONIST FOR TREATING PSYCHIATRIC DISORDERS

(57) Abstract

The present invention provides the use of a NK–1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, major depressive disorder when present with anxiety or stress disorders without concomitant therapy with other anti–depressant, anti–anxiety or anti–stress agents, methods of treatment using such a NK–1 receptor antagonist and pharmaceutical compositions comprising the same.

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# USE OF A NK-1 RECEPTOR ANTAGONIST FOR TREATING PSYCHIATRIC DISORDERS

This invention relates to the treatment or prevention of certain depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety, and stress disorders, by the administration of a NK-1 receptor antagonist, in particular, 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities. The individual may also experience changes in appetite or weight, sleep and psychomotor activity; descreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; and recurrent thoughts of death or suicidal ideation, plans or attempts. One or more major depressive episodes may give rise to a diagnosis of major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association, 1994) .

Anxiety is an emotional condition characterised by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating and tremor. It is a normal emotion but when it is severe and disabling it becomes pathological.

The condition of an individual suffering from a major depressive disorder is sometimes complicated by the fact that the individual is also suffering from anxiety. Thus in addition to the symptoms of their depressive illness, the patient may show signs of excessive or uncontrolled worry, irritability, feelings of tension, fears, restlessness and insomnia, difficulty in concentrating, and multiple somatic complaints such as pains

and aches, twitching, stiffness, myoclonic jerks, tinnitus, blurred vision, hot and cold flushes, etc., all of which add to the individual's social and occupational impairment.

Stressors have been described as physiological or psychological perturbances which disrupt an individual's homeostatic balance, and the stress-response is the set of neural and endocrine adaptations that come into effect to reestablish homeostasis (R.M. Sapolsky, "Stress, the Aging Brain, and the Mechanisms of Neuron Death", the MIT Press, Cambridge, Massachusetts, 1992). The stress-response is surprisingly convergent in that stressors as diverse as injury, starvation, temperature extremes and anxiety will provoke similar stress-responses. With prolonged stress, however, the stress-response can become as damaging as the stressor itself. Thus, chronic overactivation of the stress-response, whether due to too much stress or due to an inability to "turn-off" the stress-response, may lead to stress-related conditions including myopathy, steroid diabetes, hypertension, peptic ulcers, reproductive impairment, psychogenic dwarfism and immunosuppression.

Stress disorders may result from over-exposure to a stressor, an adjustment reaction (for example, to serious illness or breavement) or in response to an exceptionally stressful trauma.

Treatment regimens for depressive disorders commonly include the use of tricyclic anti-depressants (TCAs), monoamine oxidase inhibitors MAOIs), some psychotropic drugs, lithium carbonate, and electroconvulsive therapy (ECT) (see R. J. Baldessarini in *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Edition, Chapter 19, McGraw-Hill, 1996 for a review). More recently, new classes of anti-depressant drugs are being developed including selective serotonin reuptake inhibitors (SSRIs), specific monoamine reuptake inhibitors and 5-$HT_{1A}$ receptor agonists and antagonists.

The most established drug treatment for the management of depressive illness are the tricyclic anti-depressants. For instance,

depressed patients with prominent sleep disturbance and anxiety may be treated with a sedating tricyclic anti-depressant such as amitriptyline; for other patients, less sedating compounds such as imipramine or desipramine can be used. As well as inhibiting the uptake of noradrenaline and 5-hydroxytriptamine, tricyclic anti-depressants also possess antagonist properties at a variety of neurotransmitter receptors, including muscarinic cholinergic receptors, $\alpha_1$-adrenoceptors and $H_1$-histamine receptors. These receptor antagonist effects account for much of the side-effect profile of the tricyclic anti-depressants, and in particular, their anticholinergic side-effects which are particularly troublesome in patients with prostatic enlargement or glaucoma. Other side-effects include dry mouth, tachycardia, difficulty in visual accommodation, constipation, urinary retention, sexual dysfunction, cognitive impairment, postural hypotension, and weight gain.

Monoamine oxidase inhibitors are generally prescribed for patients who have failed to respond to tricyclic anti-depressants or electroconvulsive therapy. As with tricyclic anti-depressants, there are a number of side-effects associated with the use of MAOIs including dizziness, muscular twitching, insomnia, confusion, mania, tachycardia, postural hypotension, hypertension, dry mouth, blurred vision, impotence, peripheral oedema, hepatocellular damage and leucopenia.

Of the new classes of anti-depressant, selective serotonin reuptake inhibitors are increasingly prescribed, particularly in patients where the use of tricyclic anti-depressants is contraindicated because of their anticholinergic and cardiotoxic effects. SSRIs such as fluoxetine, fluvoxamine, sertraline and paroxetine are generally non-sedating. Furthermore, SSRIs do not stimulate appetite and may therefore be appropriate in patients in whom weight gain would be undesirable. However, SSRIs are not without their own side-effects, including nausea, diarrhoea, dry mouth, reduced appetite, dyspepsia, vomiting, headache,

nervousness, insomnia, anxiety, tremour, dizziness, fatigue, decreased libido, pharyngitis, dyspnoea, skin rash and sexual dysfunction.

Anxiety disorders are generally treated using benzodiazepine sedative-antianxiety agents. Potent benzodiazepines should not be prescribed for more than 3 or 4 weeks, however, due to the risks associated with drug dependency. Tricyclic antidepressants (TCAs) such as amitriptyline which have both anxiolytic and antidepressant actions may also be used. 5-$HT_{1A}$ receptor agonists and antagonists may also have useful anxiolytic and other psychotropic activity (see R. J. Baldessarini in *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Edition, Chapter 18, McGraw-Hill, 1996 for a review). Selective serotonin reuptake inhibitors (SSRIs) are also widely prescribed for the treatment of anxiety.

Apart from the risks of drug dependency, benzodiazepines are also associated with a number of side-effects including increased hostility and irritability, vivid or disturbing dreams, weight gain, skin rash, nausea, headache, impairment of sexual function, vertigo, and lightheadedness. Difficulties may also arise with the use of tricyclic antidepressants, in particular, due to their anticholinergic side-effects which are particularly troublesome in patients with prostatic enlargement or glaucoma. Other side-effects of tricyclic antidepressants include dry mouth, tachycardia, difficulty in visual accomodation, constipation, urinary retention, sexual dysfunction, cognitive impairment, postural hypotension, and weight gain.

SSRIs are not without their own side-effects, including nausea, diarrhoea, dry mouth, reduced appetite, dyspepsia, vomiting, headache, nervousness, insomnia, anxiety, tremour, dizziness, fatigue, decreased libido, pharyngitis, dyspnoea, skin rash and sexual dysfunction.

Apart from counselling, treatment of stress disorders may include the use of anxiolytic drugs such as benzodiazepines or tricyclic antidepressants, or hypnotic drugs. Potent benzodiazepines should not be prescribed for more than 3 or 4 weeks, however, due to the risks described

above. Also, as previously mentioned, difficulties may also arise with the use of tricyclic antidepressants (TCAs).

Selective serotonin reuptake inhibitors (SSRIs) may also be prescribed for the treatment of stress disorders but these too are not without their side-effects.

Whatever drug is used, there is a delay of usually two, three or even four weeks before a therapeutic effect is observed. This period of delay may be particularly difficult for a patient suffering from a major depressive illness, anxiety or stress.

Neurokinin 1 (NK-1; substance P) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins, and in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (see, for instance, International (PCT) patent specification Nos. WO 95/16679, WO 95/18124 and WO 95/23798).

On the other hand, European Patent Specification No. 0 286 928 describes inhibitors of the enzyme prolyl-endopeptidase, which enzyme degrades neuropeptides such as substance P, the enzyme inhibitors having an antipsychotic, anxiolytic and antidepressant action. Thus, degrading substance P or reducing the action of substance P in some other way (e.g. antagonism at its preferred NK-1 receptor) might be expected to be detrimental to the treatment of depression, anxiety, depression when present with anxiety, or stress.

More recently, International (PCT) patent specification No. WO 96/24353 (published 15th August 1996) suggests that a more efficacious and safe treatment of psychiatric disorders would be achieved using a combination of a tachykinin antagonist and a serotonin agonist or selective serotonin reuptake inhibitor (SSRI). However, such as regimen would not be free of side-effects due to the serotonin agonist or SSRI.

In view of the short-comings of existing antidepressant therapy, there is a need for new, safe and effective treatment for major depressive disorders.

The present invention provides the use of the NK-1 receptor antagonist 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof for the treatment of major depressive disorders, severe anxiety, depressive disorders when present with anxiety and stress disorders. The compounds of this class advantageously exhibit a rapid onset of action and a reduced side-effect profile when compared against conventional antidepressant, anti-anxiety and anti-stress agents.

The exceptional pharmacology of the NK-1 receptor antagonist of use in the present invention enables the treatment of major depressive disorders, severe anxiety, depressive disorders when present with anxiety and stress disorders, without the need for concomitant therapy using tricyclic antidepressants or monoamine oxidase inhibitors or, in particular, without the need for concomitant use of a serotonin agonist or antagonist or an SSRI.

Furthermore, the exceptional pharmacology of the NK-1 receptor antagonist of use in the present invention results in a rapid onset of action.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety and anti-stress agents.

The present invention also provides a method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety and anti-stress agents, which method comprises the administration to a patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention, there is provided an pharmaceutical composition for the treatment of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders which comprises essentially 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

Preferably the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)-phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof is presented in a pharmaceutical composition adapted for oral administration.

Preferably, the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)-phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof is administered once-a-day.

There exists a patient population in whom major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders are inadequately treated with existing antidepressant, anti-anxiety and anti-stress therapy. Furthermore, some patients may be adversely affected by the side-effects of tricyclic antidepressant drugs.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety and anti-stress agents in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated.

The present invention also provides a method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety and anti-stress agents in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated, which method comprises administration to a patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

In particular, there exists a patient population in whom major depressive disorders, depressive disorders when present with anxiety and

stress disorders are inadequately treated with SSRIs or serotonin agonists or antagonists. Furthermore, some patients may be adversely affected by the side-effects of SSRIs or serotonin agonists or antagonists.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents in a patient who is non-responsive to SSRIs or serotonin agonists or antagonists or for whom SSRIs or serotonin agonists or antagonists are contraindicated.

The present invention also provides a method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety and stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents in a patient who is non-responsive to SSRIs or serotonin agonists or antagonists or for whom SSRIs or serotonin agonists or antagonists are contraindicated, which method comprises administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

There also exists a patient population in whom severe anxiety disorders and stress disorders are inadequately treated with benzodiazepines. Furthermore, some patients may be adversely affected by the side-effects of benzodiazepines.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt

thereof for the manufacture of a medicament for the treatment or prevention of severe anxiety disorders or stress disorders, without concomitant therapy with other anti-anxiety or anti-stress agents, in a patient who is non-responsive to benzodiazepines or for whom benzodiazepines are contraindicated.

The present invention also provides a method for the treatment or prevention of severe anxiety disorders or stress disorders, without concomitant therapy with other anti-anxiety or anti-stress agents, in a patient who is non-responsive to benzodiazepines or for whom benzodiazepines are contraindicated, which method comprises administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

Furthermore, there exists a patient population in whom severe anxiety disorders are inadequately treated with tricyclic antidepressants. Furthermore, some patients may be adversely affected by the side-effects of tricyclic antidepressants.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of severe anxiety disorders, without concomitant therapy with other anti-anxiety agents, in a patient who is non-responsive to tricyclic antidepressants or for whom tricyclic antidepressants are contraindicated.

The present invention also provides a method for the treatment or prevention of severe anxiety disorders, without concomitant therapy with other anti-anxiety agents, in a patient who is non-responsive to tricyclic antidepressants or for whom tricyclic antidepressants are contraindicated, which method comprises administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-

bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

As used herein, the term "non-responsive" in relation to major depressive disorder means patients who have not had a reasonable clinical response (e.g. a 50% reduction in Hamilton Depression Scale (HAM-D) from a patient's baseline score after treatment with one or more clinical courses of conventional antidepressants).

As used herein, the term "non-responsive" in relation to severe anxiety disorders means patients who have not had a reasonable clinical response (e.g. a 50% reduction in Hamilton Anxiety Scale (HAM-A) from a patient's baseline score after treatment with one or more clinical courses of conventional anxiolytics).

As used herein, the term "major depressive disorder" includes single or recurrent major depressive episodes, with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset and, in the case of recurrent episodes, with or without interepisode recovery and with or without seasonal pattern.

Other mood disorders encompassed within the term "major depressive disorder" include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

A "major depressive episode" is defined as at least two weeks of depressed mood or loss of interest, which may be accompanied by other

symptoms of depression. The symptoms must persist for most of the day (i.e. for at least two thirds of the patients' waking hours), nearly every day (i.e. for at least ten out of fourteen days) for at least two consecutive weeks. A "depressed mood" is often described by the patient as feeling sad, hopeless, helpless or worthless. The patient may also appear sad to an observer, for example, through facial expression, posture, voice and tearfulness. In children and adolescents, the mood may be irritable. A "loss of interest" is often described by the patient as feeling less interested in hobbies or not feeling any enjoyment in activities that were previously considered to be pleasurable.

A major depressive episode may be accompanied by other symptoms of depression including significant weight loss when not dieting or weight gain (e.g. a change of more than 5% body weight in one month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate; or indecisiveness; and recurrent thoughts of death, recurrent suicidal ideation with or without a specific plan, or a suicide attempt.

As used herein, the term "severe anxiety disorders" includes panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, social phobias and obsessive-compulsive disorder.

"Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

"Phobias" includes agoraphobia, specific phobias and social phobias. "Agoraphobia" is characterised by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterised by clinically significant anxiety provoked by exposure to a specific feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterised by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

"Obsessive-compulsive disorder is characterised by recurrent obsessions or compulsions that are severe enough to be time consuming (i.e. they take at least one hour a day) or cause marked distress or significant impairment. At some point during the course of the disorder, the patient should recognise that the obsessions or compulsions are excessive or unreasonable.

Other anxiety disorders encompassed within the term "severe anxiety disorders" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety.

As used herein, the term "stress disorders" includes acute stress disorder, adjustment disorder and acute, chronic or delayed onset post-traumatic stress disorder.

As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the aforementioned conditions.

In particular, the NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

Full descriptions of the preparation of the NK-1 receptor antagonist which may be employed in the present invention may be found in International Patent Specification No. WO 95/18124 and US Patent No. 5,612,337.

Suitable pharmaceutically acceptable salts of the NK-1 receptor antagonist of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group.

Preferably the compositions containing the NK-1 receptor antagonist of use according to the present invention are in unit dosage forms such as tablets, pills, capsules, wafers and the like. Additionally, the NK-1 receptor antagonist of use according to the present invention may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the NK-1 receptor antagonist of use according to the present invention may be

presented in ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar

pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions of the present invention may also be administered via the buccal cavity using conventional technology, for example, absorption wafers.

Compositions in the form of tablets, pills, capsules or wafers for oral administration are particularly preferred.

A minimum dosage level for the NK-1 receptor antagonist is about 1mg per day, preferably about 5mg per day and especially about 10mg per day. A maximum dosage level for the NK-1 receptor antagonist is about 1500mg per day, preferably about 1000mg per day and especially about 500mg per day. The compounds are administered once a day.

It will be appreciated that the amount of the NK-1 receptor antagonist required for use in the treatment or prevention of major depressive disorders will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

The activity of the NK-1 receptor antagonists of use in the present invention may be measured using of the following assays:

ASSAY 1: NK-1 Receptor binding

NK-1 receptor binding assays are performed in intact Chinese hamster ovary (CHO) cells expressing the human NK-1 receptor using a modification of the assay conditions described by Cascieri *et al*, *J. Pharmacol. Exp. Ther.*, 1992, **42**, 458. Typically, the receptor is expressed at a level of $3x10^5$ receptors per cell. Cells are grown in monolayer culture, detached from the plate with enzyme-free dissociation solution (Speciality

Media Inc.), and washed prior to use in the assay. $^{125}$I-Tyr$^{8}$-substance P (0.1nM, 2000Ci/mmol; New England Nuclear) is incubated in the presence or absence of test compounds (dissolved in 5µl dimethylsulphoxide, DMSO) with $5x10^{4}$ CHO cells. Ligand binding is performed in 0.25ml of 50mM Tris-HCl, pH7.5, containing 5mM $MnCl_2$, 150mM NaCl, 0.02% bovine serum albumin (Sigma), 50µg/ml chymostatin (Peninsula), 0.1nM phenylmethylsulphonyl fluoride, 2µg/ml pepstatin, 2µg/ml leupeptin and 2.8µg/ml furoyl saccharine. The incubation proceeds at room temperature until equilibrium is achieved (>40 minutes) and the receptor-ligand complex is harvested by filtration over GF/C filters pre-soaked in 0.1% polyethylenimine using a Tomtek 96-well harvester. Non-specific binding is determined using excess substance P (1µM) and represents <10% of total binding.

ASSAY 2: Gerbil Foot-Tapping

CNS-penetrant NK-1 receptor antagonists for use in the present invention can be identified by their ability to inhibit foot tapping in gerbils induced by anxiogenic agents (such as pentagastrin) or central infusion of NK-1 receptor agonists such as GR73632, or caused by aversive stimulation such as foot shock or single housing, based on the method of Rupniak & Williams, *Eur. J. Pharmacol.*, 1994, **265**, 179.

Male or female Mongolian gerbils (35-70g) are anaesthetised by inhalation of an isoflurane/oxygen mixture to permit exposure of the jugular vein in order to permit administration of test compounds or vehicle in an injection volume of 5ml/kg i.v. Alternatively, test compounds may be administered orally or by subcutaneous or intraperitoneal routes. A skin incision is then made in the midline of the scalp to expose the skull. An anxiogenic agent (e.g. pentagastrin) or a selective NK-1 receptor agonist (e.g. GR73632 (d Ala[L-Pro$^{9}$,Me-Leu$^{10}$]-substance P-(7-11)) is infused directly into the cerebral ventricles (e.g. 3pmol in 5µl i.c.v., depending on test substance) by vertical insertion of a cuffed 27 gauge needle to a depth

of 4.5mm below bregma. The scalp incision is closed and the animal allowed to recover from anaesthesia in a clear perspex observation box (25cm x 20cm x 20cm). The duration and/or intensity of hind foot tapping is then recorded continuously for approximately 5 minutes. Alternatively, the ability of test compounds to inhibit foot tapping evoked by aversive stimulation, such as foot shock or single housing, may be studied using a similar method of quantification.

ASSAY 3: Ferret Emesis

Individually housed male ferrets (1.0 -2.5 kg) are dosed orally by gavage with test compound. Ten minutes later they are fed with approximately 100g of tinned cat food. At 60 minutes following oral dosing, cisplatin (10mg/kg) is given i.v. *via* a jugular vein catheter inserted under a brief period of halothane anaesthesia. The catheter is then removed, the jugular vein ligated and the skin incision closed. The ferrets recover rapidly from the anaesthetic and are mobile within 10-20 minutes. The animals are observed continuously during recovery from the anaesthetic and for 4 hours following the cisplatin injection, after which time the animals are killed humanely. The numbers of retches and vomits occurring during the 4 hours after cisplatin administration are recorded by trained observers.

ASSAY 4: Separation-Induced Vocalisation

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 2 weeks old. Before entering an experiment, the pups are screened to ensure that a vigorous vocalisation response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (55cm x 39cm x 19cm) in a room physically isolated from the home cage for 15 minutes and the duration of vocalisation during this baseline period is

recorded. Only animals which vocalise for longer than 5 minutes are employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 30 to 60 minutes (or for up to 4 hours following an oral dose, dependent upon the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration of vocalisation on drug treatment days is expressed as a percentage of the pre-treatment baseline value for each animal. The same subjects are retested once weekly for up to 6 weeks. Between 6 and 8 animals receive each test compound at each dose tested.

As used herein, the term "CNS-penetrant" refers to NK-1 receptor antagonists which are able to inhibit NK-1 receptor antagonist-induced foot-tapping in the gerbil as hereinafter defined.

Essentially, hind foot-tapping in the gerbil induced by infusion of the NK-1 receptor agonist, GR73632 (d Ala[L-Pro$^9$,Me-Leu$^{10}$]-substance P-(7-11)), under anaesthesia, directly into the central ventricles is inhibited when a CNS-penetrant NK-1 receptor antagonist is administered intravenously immediately prior to GR73632 challenge, wherein hind foot-tapping over a period of five minutes following recovery from the anaesthesia is inhibited with an $ID_{50} \leq 3mg/kg$, and preferably with an $ID_{50} \leq 1mg/kg$.

In an alternative method, the NK-1 receptor antagonist is administered orally, 1 hour prior to GR73632 challenge, wherein the foot-tapping over a period of five minutes following recovery from anaesthesia is inhibited with an $ID_{50} \leq 30mg/kg$, and preferably with an $ID_{50} \leq 10mg/kg$.

CNS-penetrant NK-1 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalisations by guinea-pig pups as hereinafter defined.

Essentially, a vocalisation response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated when a CNS-penetrant NK-1 receptor antagonist is administered subcutaneously 30 minutes prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an $ID_{50} \leq 20mg/kg$, preferably with an $ID_{50} \leq 10mg/kg$, and especially with an $ID_{50} \leq 5mg/kg$.

In an alternative method, the NK-1 receptor antagonist is administered orally, 4 hours prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an $ID_{50} \leq 20mg/kg$, preferably with an $ID_{50} \leq 10mg/kg$, and especially with an $ID_{50} \leq 5mg/kg$.

A suitable selection cascade for $NK_1$ antagonists of use according to the present invention is as follows:

(i) Determine affinity for human $NK_1$ receptor in radioligand binding studies (Assay 1); select compounds with $IC_{50} \leq 10nM$, preferably $IC_{50} \leq 2nM$, especially $IC_{50} \leq 1nM$.

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit foot tapping in gerbils induced by central injection of an $NK_1$ agonist (Assay 2); select compounds that inhibit foot tapping with $ID_{50} \leq 3mg/kg$ i.v., and preferably $ID_{50} \leq 1mg/kg$ i.v. when administered immediately prior to central $NK_1$ agonist challenge, or $ID_{50} \leq 30mg/kg$ p.o., and preferably $ID_{50} \leq 10mg/kg$ p.o. 1 hour prior to challenge.

(iii) Determine central duration of action of compounds in gerbil foot tapping assay following intravenous administration 24 hours prior to central $NK_1$ agonist challenge; select compounds showing $\leq$ 25-fold loss of potency compared with $ID_{50}$ determined in step (ii) above with the proviso that $ID_{50} \leq 10mg/kg$ i.v., and preferably $\leq 5mg/kg$ i.v. after 24 hour pre-treatment.

(iv) Determine oral bioavailability of compounds by pharmacokinetic analysis, activity in gerbil foot tapping assay following oral administration and/or by ability to inhibit cisplatin-induced emesis in ferrets (Assay 3);

select compounds with $ID_{90} \leq 3$mg/kg p.o., and preferably $ID_{90} \leq 1$mg/kg p.o.

Particularly preferred compounds of use in the present invention are identified using steps (i) to (iv) followed by step (v):

(v) Determine activity of compounds in assays sensitive to conventional antipsychotic drugs (inhibition of distress vocalisations in guinea-pig pups (Assay 4)). Select compounds with $ID_{50} \leq 20$mg/kg, and preferably $ID_{50} \leq 10$mg/kg.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NK-1 receptor binding criteria of step (i) which, in addition, have ≤ 5-fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

The NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, the preparation of which is described in International Patent Specification No. WO 95/18124 and US Patent No. 5,612,337. In the aforementioned assays, this compound has the following activity:

| | |
|---|---|
| human NK-1 receptor binding: | $IC_{50} = 0.12$ nM |
| gerbil foot-tapping (5 mins.): | $ID_{50} = 0.38$ mg/kg i.v. |
| gerbil foot-tapping (24 hrs.): | $ID_{50} = 2.2$ mg/kg i.v. |
| ferret emesis: | $ID_{90} = 1$ mg/kg p.o. |
| guinea-pig vocalisation (4 hr. pre-treatment): | $ID_{50} = 0.91$ mg/kg p.o. |

The following example illustrates pharmaceutical compositions according to the present invention.

EXAMPLE 1 Tablets containing 50-300mg of NK-1 antagonist

| | Amount mg | | |
|---|---|---|---|
| NK-1 antagonist | 50.0 | 100.0 | 300.0 |
| Microcrystalline cellulose | 80.0 | 80.0 | 80.0 |
| Modified food corn starch | 80.0 | 80.0 | 80.0 |
| Lactose | 189.5 | 139.5 | 139.5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 |

The active ingredient, cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 50mg, 100mg and 300mg of the NK-1 receptor antagonist per tablet.

CLAIMS:

1. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents.

2. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents, in a patient who is non-responsive to heterocyclic anti-depressants, SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic anti-depressants, SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated.

3. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents, in a patient who

is non-responsive to SSRIs or serotonin agonists or antagonists or for whom SSRIs or serotonin agonists or antagonists are contraindicated.

4. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of severe anxiety disorders or stress disorders without concomitant therapy with other anti-anxiety or anti-stress agents, in a patient who is non-responsive to benzodiazepines or for whom benzodiazepines are contra-indicated.

5. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of severe anxiety disorders, without concomitant therapy with other anti-anxiety agents, in a patient who is non-responsive to tricyclic antidepressants or for whom tricyclic antidepressants are contraindicated.

6. A pharmaceutical composition for the treatment of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders, which comprises essentially 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

7. A method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other

antidepressant, anti-anxiety or anti-stress agents, which method comprises the administration to a patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

8. A method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents in a patient who is non-responsive to heterocyclic anti-depressants, SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic anti-depressants, SSRIs, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated, which method comprises administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

9. A method for the treatment or prevention of major depressive disorders, severe anxiety disorders, depressive disorders when present with anxiety or stress disorders without concomitant therapy with other antidepressant, anti-anxiety or anti-stress agents in a patient who is non-responsive to SSRIs or serotonin agonists or antagonists, or for whom SSRIs or serotonin agonists or antagonists are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

10. A method for the treatment or prevention of severe anxiety disorders or stress disorders without concomitant therapy with other anti-anxiety or anti-stress agents, in a patient who is non-responsive to benzodiazepines or for whom benzodiazepines are contraindicated, which method comprises administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

11. A method for the treatment or prevention of severe anxiety disorders, without concomitant therapy with other anti-anxiety agents, in a patient who is non-responsive to tricyclic antidepressants or for whom tricyclic antidepressants are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

12. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the major depressive disorder is selected from single or recurrent major depressive episodes, with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset and, in the case of recurrent episodes, with or without interepisode recovery and with or without seasonal pattern.

13. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the major depressive disorder is selected from dysthymic disorder with early or late onset and with or without atypical features; dementia of

the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

14. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the major depressive disorder results from a general medical condition.

15. A use, composition or method as claimed in claim 14 wherein the general medical condition is selected from myocardial infarction, diabetes, miscarriage or abortion.

16. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the severe anxiety disorder is selected from panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, social phobias or obsessive-compulsive disorders.

17. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the severe anxiety disorder is selected from anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety.

18. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11

wherein the anxiety present with the major depressive disorder is generalised anxiety.

19. A use, composition or method according to claim 18 wherein the generalised anxiety also includes panic disorders, phobias or stress disorders.

20. A use according to any one of Claims 1 to 5, or a composition according to Claim 6 or a method according to any one of Claims 7 to 11 wherein the stress disorder is selected from acute stress disorder, adjustment disorder and acute, chronic or delayed onset post-traumatic stress disorder.

# INTERNATIONAL SEARCH REPORT

In' ational Application No
PCT/GB 99/01797

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6 A61K31/535

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. |
|---|---|---|
| X,P | WO 98 24441 A (MERCK SHARP & DOHME ) 11 June 1998 (1998-06-11) claims 1-15 --- | 1-20 |
| X,P | WO 98 24439 A (MERCK SHARP & DOHME ) 11 June 1998 (1998-06-11) claims 1-13 --- | 1-20 |
| X,P | WO 98 24438 A (MERCK SHARP & DOHME ) 11 June 1998 (1998-06-11) the whole document --- | 1-20 |
| X,P | WO 98 24440 A (MERCK SHARP & DOHME ) 11 June 1998 (1998-06-11) claims 1-10 --- | 1-20 |

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[X] Further documents are listed in the continuation of box C.

[X] 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 13 September 1999 | 21/09/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Siatou, E |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,P | WO 98 24444 A (MERCK SHARP & DOHME)<br>11 June 1998 (1998-06-11)<br>claims 1-9 | 1-20 |
| X | WO 95 18124 A (MERCK SHARP & DOHME)<br>6 July 1995 (1995-07-06)<br>cited in the application<br>claims 9,16-18,22<br>page 19, line 12 - line 13<br>page 30, line 22 - line 26<br>page 31, line 12 - line 14 | 1-20 |
| A | WO 98 15277 A (MERCK SHARP & DOHME)<br>16 April 1998 (1998-04-16)<br>claims 1-5,7,11-18,25,26 | 1-20 |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01797

## 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 7-11 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/GB 99/01797

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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