A combination product containing flecainide and modafinil.

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(57) Abstract: The present invention relates to the use of flecainide as an anti-connexin agent. This anti-connexin agent is advantageous used to potentiate the therapeutic effect of various psychotropic drugs. More specifically, the invention provides a combination product containing flecainide and modafinil.

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USE OF FLECAINIDE AS AN ANTI-CONNEXIN AGENT AND METHOD FOR POTENTIATING THE EFFECTS OF A PSYCHOTROPIC DRUG

Summary of the invention

The present invention relates to the use of flecainide as an anti-connexin agent. This anti-connexin agent is advantageously used to potentiate the therapeutic effect of various psychotropic drugs. More specifically, the invention provides a combination product containing flecainide and modafnil.

Background of the invention

Gap junctions are involved in intercellular communication, which is important for maintaining tissue and organ homeostasis. Gap junctions connect the cell cytoplasm, enabling the exchange of ions (Ca\(^{+}\) and K\(^{+}\)), second messengers (AMPc, GMPc, IP3), several small metabolites (glucose) and ensuring electrical and metabolic coupling between the cells. The gap junctions are junctions with a selective permeability, formed by protein channels contained in the plasma membrane, and formed by connexin hexamers. Connexin hexamers might as well form hemichannel, linked the intracellular space to extracellular one.

Connexins are integral proteins of the plasma membrane, which are synthesized by practically every cell type, regardless of the position of a multicellular organism in the phylogenesis of the animal world. In vertebrates, occasional cells not producing connexins are adult striated muscle cells, spermatozoids and circulating blood cells. Unlike numerous membrane proteins, connexins have a short half-life (between 3 and 6 hours), are not glycosylated and do not have an enzymatic activity. At present, at least thirteen distinct connexins have been identified in mammals; corresponding, in humans, to 21 isoforms. In practice, various types of connexins can be present in a plurality of tissues, and most of the cells synthesize a plurality of connexins. Before reaching the cell membrane, the connexins assemble in groups of six molecules to form hollow tubular structures called connexons,
which join the plasma membrane by means of Golgi vesicles. When cell contact is established, the connexons of a cell align end-to-end with those of the neighboring cell, establishing a continuous hydrophilic channel around 10 nm long. This junctional channel establishes direct contact between the cytoplasms of the two cells in contact, over the intercellular space.

Connexins are involved in a huge number of physiological processes, and several applications of connexin blocking agents (also called hereafter "connexin blocking agents" or "anti-connexin agents") have been described.

For example, anti-connexin agents have been proposed for treating and/or preventing the following conditions:

- cancers (WO2006/134494 and WO2006/049157),
- some cardiovascular diseases (WO2006/134494),
- wounds (WO2006/134494 and WO2009/097077),
- pain (WO2009/148613),
- migraines (Durham and Garrett, 2009),
- epilepsy (Juszczak and Swiergiel, 2009),
- neurological conditions (WO2006/134494) and neurodegenerative diseases (Takeuchi et al. 2011),
- ischemia (Davidson et al, 2013),
- drug-induced liver injury (Patel et al, 2012)
- infectious diseases (WO2011/067607),
- cytotoxicity induced by chemotherapeutic agents (Tong X. et al, 2013)
    and

Furthermore, the present inventors previously described that anti-connexin agents are able to potentiate the therapeutic effects of psychotropic drugs (WO 2010/029131). In particular, they described that administration of anti-connexin agents such as meclofenamic acid (MFA) increases the therapeutic effects of various psychotropic molecules, enabling to reduce the active doses and thus the undesirable effects of these psychotropic molecules. These synergistic effects have been observed with a wide range of
psychotropic molecules (clozapine, paroxetine, modafnil, diazepam, venlafaxine, escitalopram, bupropion and sertraline).

Identifying new anti-connexin agents is therefore of primary importance to highlight new therapeutic tools aiming to treat various diseases and disorders, in particular in combination with psychotropic drugs.

In this context, the inventors have now demonstrated that the well-known antiarrhythmic agent flecainide, has a broad anti-connexin activity. This is a very surprising result, since flecainide had been described so far to interfere with sodium channels, in particular on heart muscle cells, and these channels are not related with brain gap junctions. Moreover, flecainide had been shown not to influence junctional resistance of cardiac myocyte cell pairs (Daleau et al. 1998).

**Detailed description of the invention**

In the context of the invention, "flecainide" designates a compound of formula \(N-(\text{piperidin-2-ylmethyl})-2,5\text{-bis(2,2,2-trifluoroethoxy)}\) benzamide. As used herein, this term designates any form of this compound, such as a salt thereof. Preferably, said salt is the flecainide acetate. This term may also encompass the flecainide precursors which can be metabolized in the human body and/or its derivatives (for example, chemical derivatives resulting from one or several halogen substitutions and/or from addition of protective groups).

As disclosed on figure 5A and 5B, flecainide possesses a chiral center implying the existence of an R and S enantiomers (\((S)-\)flecainide and \((R)-\)flecainide). Figure 5 shows the formulas of R-flecainide (Fig. 5A, \((i \neq)-N-(\text{piperidin-2-ylmethyl})-2,5\text{-bis(2,2,2-trifluoroethoxy)}\) benzamide) and S-flecainide (Fig. 5B, \((S)-N-(\text{piperidin-2-ylmethyl})-2,5\text{-bis(2,2,2-trifluoroethoxy)}\) benzamide).

As used herein, the term "flecainide" designates the racemate form of \(N-(\text{piperidin-2-ylmethyl})-2,5\text{-bis(2,2,2-trifluoroethoxy)}\) benzamide, as well as the R and S enantiomers thereof \((i \neq)-N-(\text{piperidin-2-ylmethyl})-2,5\text{-bis(2,2,2-trifluoroethoxy)}\) benzamide and \((S)-N-\).
(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide, respectively). In a preferred embodiment of the invention, the R enantiomer of flecainide ((i?-)-N-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide) will be used.

Flecainide is currently administered as a racemate (Kroemer et al, 1989; Lie et al, 1989). The pharmacokinetic parameters of the two enantiomers of flecainide have been largely described, after administration in human and rodents, as described below:

In 1989, Kroemer et al. published a study in 13 patients receiving long-term oral flecainide therapy. S-flecainide and R-flecainide plasma levels were determined, and plasma concentrations of R-flecainide were significantly higher than those of the S-flecainide enantiomer (R/S ratio = 1.10), suggesting that the flecainide drug undergoes modest enantioselective disposition [Kroemer et al, 1989].

In 1989, Gross et al. compared the disposition of the two enantiomers in two human populations: extensive (EM) and five poor (PM) metabolizers of sparteine/debrisoquine after administration of 50mg of racemic flecainide acetate [Gross et al, 1989]. Gross et al. presented data indicating that the half-life of R-flecainide (12.9h) was longer (P< 0.03) than that of S-flecainide (9.8h). The renal clearance of the two enantiomers was, however, comparable and similar to that observed in the EM subjects. The urinary recovery of R-flecainide (15.6± 3.7mg) was greater (P< 0.03) than that of the S-enantiomer (12.0 ± 3.7 mg). The enantioselective disposition observed in PMs is therefore due to greater impairment in the metabolism of R-flecainide than S-flecainide.

In 1991, Alessi-Severini et al. summarized key findings on pharmacokinetics and concluded that there was no evidence of enantioselective disposition of flecainide in human [Alessi-Severini et al, 1991], citing three reports on stereoselective therapeutic monitoring, which found R/S ratio ranges of 0.67-1.39 (mean 1.03 ± 0.16), 0.75-1.44 (mean 1.04), and 0.89-1.32 (mean 1.10 ± 0.13), and that Gross et al. 1989 study was not relevant on the total population.

In 1998, Hanada et al. demonstrated an absence of enantioselective distribution of the two enantiomers of flecainide in several tissue, after intravenous administration of flecainide racemate in rats [Hanada et al, 1998].
As reviewed in [Mehvar et al, 2002], it appears that the renal clearances of the enantiomers of flecainide are not stereoselective in both healthy volunteers and patients.

Literature is thus globally coherent on the absence of stereoselective effects of flecainide on pharmacokinetics and metabolism.

The physicochemical properties of the two enantiomers of flecainide have been also described. In particular, Turgeon et al. described a stereoselective analytical method for the determination of the antiarrhythmic agent flecainide in human plasma. The resolution of the enantiomers is achieved by high-performance liquid chromatography (HPLC) on a normal phase silica column following derivatization with the optically active reagent (−)-methyl chloroformate [Turgeon et al, 1990].

Moreover, Alessi-Severini et al. described a stereospecific high-performance liquid chromatographic method for the determination of (R,S)-flecainide acetate in human plasma and urine. Flecainide diastereomers were separated after i) a single-step extraction of alkalinized samples performed with distilled diethyl ether, ii) the organic layer was evaporated and the drug was derivatized with 1-[(4-nitrophenyl)sulfonyl]-L-propyl chloride at 80 degrees C for 2 h and iii) by high-performance liquid chromatography (HPLC) on a C18 reversed-phase column with a mobile phase consisting of acetonitrile:water:triethylamine (45:55:0.2) at a flow rate of 1 mL/min [Alessi-Severini et al, 1990].

Racemic flecainide acetate is a widely used class 1c antiarrhythmic agent, which is indicated for treating various types of arrhythmias. More specifically, it is used to regulate the rate and rhythm of the heart. The heart's pumping action is controlled by electrical signals that pass through the heart muscle. These electrical signals cause the two pairs of heart chambers (left and right arteria and ventricles) to contract in a regular manner to produce regular heartbeats. If the electrical activity in the heart is disturbed for any reason, irregular heartbeats (arrhythmias) of various types can result. Flecainide helps to treat arrhythmias by decreasing the sensitivity of the heart muscle cells to electrical impulses.

This regulates the electrical conduction in the heart muscle and reduces disturbances in the heart rhythm. As a class I antiarrhythmic agent, flecainide interferes with the sodium channel.
Importantly, several studies have demonstrated that these cardiovascular effects are not mediated by a single enantiomer, both of them contributing to cardiovascular functions:

Antiarrhythmic effects of flecainide and its enantiomers were assessed in two different animal models, chloroform-induced ventricular fibrillation in mice and ouabain-induced ventricular tachycardia in dogs. The two enantiomers were highly effective in suppressing both of these experimental arrhythmias and appeared to be essentially equipotent. No significant differences were found either between the two enantiomers or between the enantiomers and racemic flecainide [Banitt et al, 1986].

The effects of the enantiomers on action potential characteristics in canine cardiac Purkinje fibers were assessed, and they were shown to exert similar electrophysiological effects [Kroemer et al, 1989].

The effects of flecainide acetate racemate and its two enantiomers on voltage-operated sodium and potassium channels and on the sodium pump activity of non-myelinated fibers of the guinea-pig vagus nerve were studied with the sucrose-gap method. There was no significant difference in the effect caused by the enantiomers separately [Lie et al, 1989].

The effects of the enantiomers were evaluated in isolated canine Purkinje fibers using standard microelectrode techniques. The results suggest there is no significant difference between the effects of flecainide enantiomers on basic electro-physiological parameters of canine Purkinje fibers [Smallwood et al, 1989].

To conclude, all those studies have provided no evidence to indicate that administration of a single enantiomer, rather than the racemic drug, would offer any advantage.

According to a first aspect, the present invention therefore pertains to the use of flecainide, *in vitro* and *in vivo*, as an anti-connexin agent. In particular, the present invention relates to flecainide for use as an anti-connexin agent, or, in other words, for blocking gap junctions.

There are 21 genes coding for different connexin isoforms in humans, and different combinations of connexin monomers involved in the composition of the gap junctions are described. In particular, the connexins 26 (Cx 26), 30 (Cx 30), 30.2 (Cx30.2), 32 (Cx 32),...
36 (Cx 36), 37 (Cx 37), 40 (Cx 40), 43 (Cx 43), 45 (Cx 45), 46 (Cx 46), and 47 (Cx 47) are expressed in human on cells of the Central or Peripheral Nervous System (Nakase & Naus, 2004).

The present inventors observed that flecainide is effective for inhibiting gap junctions made of all connexin they tested. In particular, and as disclosed in the experimental part below, flecainide is effective for inhibiting gap junctions made of connexin Cx40, Cx26, Cx30, Cx32, and/or Cx43. Importantly, this anti-connexin effect is similar to the one observed for well-known anti-connexin agents such as mefloquine and meclofenamic acid (MFA) (Juszczał & Swiergiel, 2009; Cruikshank et al, 2004; Harks et al, 2001). Higher inhibition levels were even reached for glial connexins Cx26, Cx30 and Cx43 (see figure 1).

The present invention therefore relates to the in vitro use of flecainide as an anti-connexin agent. Preferably, this agent can be used to inhibit gap junctions made of the connexins selected in the group consisting of: Cx23 (SEQ ID NO:1), Cx25 (SEQ ID NO:2), Cx26 (SEQ ID NO:3), Cx 30 (SEQ ID NO:4), Cx30.2 (SEQ ID NO:5), Cx30.3 (SEQ ID NO:6), Cx31 (SEQ ID NO:7), Cx31.1 (SEQ ID NO:8), Cx31.9 (SEQ ID NO:9), Cx32 (SEQ ID NO:10), Cx36 (SEQ ID NO:11), Cx37 (SEQ ID NO:12), Cx40 (SEQ ID NO:13), Cx40.1 (SEQ ID NO:14), Cx43 (SEQ ID NO:15), Cx45 (SEQ ID NO:16), Cx46 (SEQ ID NO:17), Cx47 (SEQ ID NO:18), Cx50 (SEQ ID NO:19), Cx59 (SEQ ID NO:20), and Cx62 (SEQ ID NO:21).

In a preferred embodiment of the invention, flecainide is used for blocking one or more of the connexins expressed in human cells of the Central or Peripheral Nervous System, that are selected in the group consisting of: Cx 26 (SEQ ID NO:3), Cx 30 (SEQ ID NO:4), Cx30.2 (SEQ ID NO:5), Cx 32 (SEQ ID NO:10), Cx36 (SEQ ID NO:11), Cx 37 (SEQ ID NO:12), Cx40 (SEQ ID NO:13), Cx43 (SEQ ID NO:15), Cx 45 (SEQ ID NO:16), Cx 46 (SEQ ID NO:17) and Cx 47 (SEQ ID NO:18).

In a more preferred embodiment, flecainide is used for blocking one or more of the connexins selected in the group consisting of: Cx40 (SEQ ID NO:13), Cx26 (SEQ ID NO:3), Cx30 (SEQ ID NO:4), Cx32 (SEQ ID NO:10), and Cx43 (SEQ ID NO:15).
In an even more preferred embodiment, flecainide is used for blocking one or more of the connexins selected in the group consisting of: Cx26 (SEQ ID NO:3), Cx30 (SEQ ID NO:4) and Cx43 (SEQ ID NO:15).

Due to its anti-connexin activity, flecainide can be used for the treatment of a number of disorders and conditions known to benefit from treatment by anti-connexin molecules.

These disorders and conditions include, but are not limited to: cancers, cardiovascular diseases, wounds, pain, migraines, epilepsy, neurological conditions and neurodegenerative diseases, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, ischemia and inflammatory disorders.

More preferably, flecainide can be used for the prevention and/or the treatment of cancers, wounds, migraines, epilepsy, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, ischemia and inflammatory disorders.

Even more preferably, flecainide can be used for the prevention and/or the treatment of wounds, migraines, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia.

Even more preferably, flecainide can be used for the prevention and/or the treatment of drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia.

According to a particular aspect of the present invention, flecainide is used as an agent for potentiating the effects of a psychotropic drug. These potentiating effects are illustrated below by experiments performed with modafnil (see figures 2 to 4). As an anti-connexin agent, flecainide can potentiate the effects of any psychotropic drug (as shown in WO 2010/029131 and US 2011/1 72 188, incorporated by reference).

The term "potentiate" in this case means that flecainide significantly increases the therapeutic effects of the psychotropic drug administered to the same patient. Thus, the combination of the psychotropic drug with flecainide makes it possible to reduce the doses of said psychotropic drug and therefore to limit the adverse effects of said psychotropic drug, and/or to obtain a stronger therapeutic effect without increasing the dose of said psychotropic drug.
In the present text, a "psychotropic drug" or "psychotropic agent" refers to any substance that acts primarily on the state of the central nervous system by modifying certain cerebral biochemical and physiological processes. Examples of psychotropic drugs which can be used in the context of the present invention include anesthetics, analgesics such as opioids, antipyretics and antimigraine preparations, anti-epileptics, anti-Parkinson drugs such as anti-cholinergic and dopaminergic anti-Parkinson agents, psycholeptics such as antipsychotics, anxiolytics, hypnotics and sedatives, psychoanaleptics such as antidepressants, psychostimulants and anti-dementia drugs, as well as parasympatomimetics, anti-addiction drugs, antivertigo preparations etc. Non-limitative examples of specific molecules which can be advantageously used as psychotropic drugs according to the invention are listed in Table 1 below.

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Pharmacological sub-class</th>
<th>Chemical sub-class</th>
<th>Active agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetics</td>
<td>1. General anesthetics</td>
<td>2. Ethers</td>
<td>3. diethyl ether; vinyl ether</td>
</tr>
<tr>
<td></td>
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<td>4. Halogenated hydrocarbons</td>
<td>5. halothane; chloroform; enflurane; trichloroethylene; isoflurane; desflurane; sevoflurane</td>
</tr>
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<td></td>
<td></td>
<td>6. Barbiturates, plain</td>
<td>7. methohexital; hexobarbital;</td>
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<td></td>
<td></td>
<td>8. Barbiturates in combination with other drugs</td>
<td>9. narcobarbital</td>
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<tr>
<td></td>
<td></td>
<td>10. Opioid anesthetics</td>
<td>11. fentanyl; alfentanil; sufentanil; phenoperidine; anileridine; remifentanil;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Other general anesthetics</td>
<td>13. droperidol; ketamine; propanidid; alfaxalone; etomidate; propofol; sodium oxybate; nitrous oxide; esketamine; xenon;</td>
</tr>
<tr>
<td></td>
<td>14. Local anesthetics</td>
<td>15. Esters of aminobenzoic acid</td>
<td>16. metabolthamine; procaine; tetracaine; chloroprocaine; benzocaine;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17. Amides</td>
<td>18. bupivacaine; lidocaine; mepivacaine; prilocaine; butanilicaine; cinchocaine; etidocaine; articaine; ropivacaine; levobupivacaine; bupivacaine;</td>
</tr>
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<td></td>
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<td>19. Esters of benzoic acid</td>
<td>20. cocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21. Other local anesthetics</td>
<td>22. ethyl chloride; dyclonine; phenol; capsaicin;</td>
</tr>
<tr>
<td>Analgesics</td>
<td>23. Opioids</td>
<td>24. Natural opium alkaloids</td>
<td>25. opium; hydromorphone; nicomorphine; oxycodone; dihydrocodeine; diamorphine; papaveretum; morphine; codeine,</td>
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<tr>
<td>26. Phenylpiperidine derivatives</td>
<td>27. ketobemidone; pethidine;</td>
<td></td>
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<tr>
<td>28. Diphenylpropylamine derivatives</td>
<td>29. dextromoramide; piritramide; dextropropoxyphene; bezitramide; methadone,</td>
<td></td>
<td></td>
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<tr>
<td>30. Benzomorphan derivatives</td>
<td>31. pentazocine; phenazocine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Morphinan derivatives</td>
<td>33. butorphanol; nalbuphine</td>
<td></td>
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<tr>
<td>34. Other opioids</td>
<td>35. tilidine; tramadol; dezocine; meptazinol; tapentadol;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Other analgesics and antipyretics</td>
<td>37. Salicylic acid and derivatives</td>
<td>38. acetylsalicylic acid; aloxiprin; choline salicylate; sodium salicylate; salicylamide; salsalate; ethenazamide; morpholine salicylate; dipyrocetyl; benorilate; diflunisal; potassium salicylate; guacetisal; carbasalate calcium; imidazole salicylate</td>
<td></td>
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<tr>
<td>39. Pyrazolones</td>
<td>40. phenazone; metamizole sodium; aminophenazone ; propyphenazone; nifenazone;</td>
<td></td>
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<tr>
<td>41. Anilides</td>
<td>42. paracetamol; phenacetin; bucetin; propacetamol ;</td>
<td></td>
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<tr>
<td>43. Other analgesics and antipyretics</td>
<td>44. rimazolium; glafenine; floctafenine; viminol; nefopam; ziconotide; methoxyflurane; nabiximols</td>
<td></td>
<td></td>
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<tr>
<td>45. Antimigraine Preparations</td>
<td>46. Ergot alkaloids</td>
<td>47. Dihydroergotamine; ergotamine; methysergide; lisuride;</td>
<td></td>
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<tr>
<td>48. Corticosteroid derivatives</td>
<td>49. flumedroxone</td>
<td></td>
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</tr>
<tr>
<td>50. Selective serotonin (5HT1) agonists</td>
<td>51. sumatriptan; naratriptan; zolmitriptan; rizatriptan; almotriptan; eletriptan; frovatriptan</td>
<td></td>
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<tr>
<td>52. Other antimigraine preparations</td>
<td>53. pizotifen; clonidine; iprazochrom; dimetotizaine ; oxetorone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>54. Antiepileptics</td>
<td>55. Barbiturates and derivatives</td>
<td>56. methylphenobarbital; Phenobarbital; primidone; barbexaclone; metharbital</td>
</tr>
<tr>
<td>57. Hydantoin derivatives</td>
<td>58. ethotoxin; phentoin; amino(diphenylhydantoin) valeric</td>
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</tr>
<tr>
<td>Anti-Parkinson drugs</td>
<td>71. Anticholinergic agents</td>
<td>72. Tertiary amines</td>
<td>73. Trihexyphenidyl; biperiden; metixene; procyclidine; profenamine; dextemidide; phenglutarimidine; mazaticol; bornaprine; tropatpine</td>
</tr>
<tr>
<td>74. Ethers chemically close to antihistamines</td>
<td>75. etanautine; orphenadrine</td>
<td></td>
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<tr>
<td>76. Ethers of tropine or tropine derivatives</td>
<td>77. benztropine; etybenztropine</td>
<td></td>
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<tr>
<td>78. Dopaminergic agents</td>
<td>79. Dopa and dopa derivatives</td>
<td>80. levodopa; decarboxylase inhibitor; COMT inhibitor; melevodopa ; etilevodopa</td>
<td></td>
</tr>
<tr>
<td>81. Adamantan derivatives</td>
<td>82. amantadine</td>
<td></td>
<td></td>
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<tr>
<td>83. Dopamine agonists</td>
<td>84. bromocriptine; pergolide; dihydroergocryptine; esylate; ropinirole; pramipexole; cabergoline; apomorphine; piribedil; rotigotine</td>
<td></td>
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<tr>
<td>85. Monoamine oxidase B inhibitors</td>
<td>86. selegiline; rasagiline</td>
<td></td>
<td></td>
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<tr>
<td>87. Other dopaminergic agents</td>
<td>88. olcapone; entacapone; budipine</td>
<td></td>
<td></td>
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<tr>
<td>Psycho-leptics</td>
<td>89. Antipschotics</td>
<td>90. Phenothiazines with</td>
<td>91. chlorpromazine; levomepromazine; promazine;</td>
</tr>
<tr>
<td></td>
<td><strong>aliphatic side-chain</strong></td>
<td>acepromazine; triflupromazine; cyamemazine; chlorproethazine</td>
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<tr>
<td><strong>92. Phenothiazines with piperazine structure</strong></td>
<td><strong>93.</strong> dixyrazine; fiuphenazine; perphenazine; prochlorperazine; thioproperazine; trifluoperazine; acetophenazine; thioproperazine; butaperazine; perazine</td>
<td></td>
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<tr>
<td><strong>94. Phenothiazines with piperidine structure</strong></td>
<td><strong>95.</strong> perciazine; thioridazine; mesoridazine; pipotiazine</td>
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<tr>
<td><strong>96. Butyrophenone derivatives</strong></td>
<td><strong>97.</strong> Haloperidol; trifluperidol; melperone; moperone; pipamperone; bromperidol, benperidol; droperidol; fluanisone</td>
<td></td>
<td></td>
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<tr>
<td><strong>98. Indole derivatives</strong></td>
<td><strong>99.</strong> oxypertine; molindone; sertindole; ziprasidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>100. Thioxanthene derivatives</strong></td>
<td>/0/. fiupentixol; clopentixol; chlorprothixene; tiotixene; zuclopentixol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>102. Diphenylbutylpiperidine derivatives</strong></td>
<td>/03. fluspirilene; pimozide; penfluridol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>104. Diazepines, oxazepines, thiazepines and oxepines</strong></td>
<td>/05.1oxapine; clozapine; olanzapine; quetiapine; asenapine; clotiapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>106. Benzamides</strong></td>
<td><strong>107.</strong> sulpiride; sultopride; tiapride; remoxipride; amisulpride; veralipride; levosulpiride</td>
<td></td>
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<tr>
<td><strong>108. Lithium</strong></td>
<td><strong>109.</strong> lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>110. Other antipsychotics</strong></td>
<td><strong>111.</strong> prothipendyl; risperidone; mosapramine; zotepine; aripiprazole; paliperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>112. Anxiolytics</strong></td>
<td><strong>113.</strong> Benzodiazepine derivatives</td>
<td><strong>114.</strong> chlordiazepoxide; medazepam; oxazepam; potassium clorazepate; lorazepam; adinazolam; bromazepam; clobazam; ketazolam; prazepam; alprazolam; halazepam; pinazepam camazepam; nordazepam; fluidazepam; ethyl lofazepate; etizolam; clotiazepam; cloxazolam; tofisopam</td>
<td></td>
</tr>
<tr>
<td><strong>115. Diphenylthene derivatives</strong></td>
<td><strong>116.</strong> hydroxyzine; captodiame;</td>
<td></td>
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<tr>
<td><strong>117. Carbamates</strong></td>
<td>118. meprobamate; emylcamate; mebutamate;</td>
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<tr>
<td>119.</td>
<td>Dibenzo-bicyclo-octadiene derivatives</td>
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<tr>
<td>120.</td>
<td>benzoctamine</td>
<td></td>
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<tr>
<td>121.</td>
<td>Azaspirodec anedione derivatives</td>
<td></td>
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<tr>
<td>122.</td>
<td>buspirone</td>
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<tr>
<td>123.</td>
<td>Other anxiolytics</td>
<td></td>
<td></td>
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<tr>
<td>124.</td>
<td>Mephenoxaline; gedocarnil; etifoxine</td>
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<tr>
<td>125.</td>
<td>Hypnotics and sedatives</td>
<td></td>
<td></td>
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<tr>
<td>126.</td>
<td>Barbiturates, plain</td>
<td></td>
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<tr>
<td>127.</td>
<td>Pentobarbital; amobarbital; butobarbital; barbital; aprobabital; secobarbital; talbutal; vinylbital; vinbarbital; cyclobarbital; heptabarbital; reposal; methohexitol; thiopental; etallobarbital; allobarbital; proxibarbal</td>
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<tr>
<td>128.</td>
<td>Aldehydes and derivatives</td>
<td></td>
<td></td>
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<tr>
<td>129.</td>
<td>chloral hydrate; chloralodol; acetylglycinamide; dichloralphenazone; paraldehyde</td>
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<tr>
<td>130.</td>
<td>Benzodiaze pine derivatives</td>
<td></td>
<td></td>
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<tr>
<td>131.</td>
<td>flurazepam; nitrazepam; flunitrazepam; estazolam; triazolam; lormetazepam; temazepam; midazolam; brotizolam; quazepam; loprazolam; doxefazepam; cinotazepam</td>
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<tr>
<td>132.</td>
<td>Piperidinedione derivatives</td>
<td></td>
<td></td>
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<tr>
<td>133.</td>
<td>glutethimide; methyprylon; pyrithyldione</td>
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<tr>
<td>134.</td>
<td>Benzodiaze pine related drugs</td>
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<tr>
<td>135.</td>
<td>zopiclone; Zolpidem; zaleplon; eszopiclone</td>
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<tr>
<td>136.</td>
<td>Melatonin receptor agonists</td>
<td></td>
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<tr>
<td>137.</td>
<td>melatonin; ramelteon</td>
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<tr>
<td>138.</td>
<td>Other hypnotics and sedatives</td>
<td></td>
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<tr>
<td>139.</td>
<td>methaqualone; clomethiazole; bromisoval; carbromal; scopalamine; propiomazine; triclofos ethchlorvynol; valerian; hexapropymate; bromides; apronal; valnoctamide; methylpentynol; niaprazine; dexametomidine</td>
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<tr>
<td>140.</td>
<td>Hypnotics and sedatives in combination, excl. barbiturates</td>
<td></td>
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<tr>
<td>141.</td>
<td>emepronium; dipiperonylamino ethano 1</td>
<td></td>
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<tr>
<td>Psychoana-leptics</td>
<td>142.</td>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>143.</td>
<td>Non-selective monoamine reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>144.</td>
<td>desipramine; imipramine; imipramine oxide; clomipramine; opipramol; trimipramine; lofepramine; dibenzepin; amitriptyline; nortriptyline;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 145. | Selective serotonin reuptake inhibitors | 146. | zimeldine; fluoxetine; 
citalopram; paroxetine; sertraline; 
alaproclate; fluvoxamine; 
etoperidone; escitalopram |
| 147. | Monoamine oxidase inhibitors, non-selective | 148. | isocarboxazid; nialamide; 
phenelzine; tranylcypromine; 
iproniazide; iproclozide |
| 149. | Monoamine oxidase A inhibitors | 150. | moclobemide; toloxatone |
| 151. | Other antidepressants | 152. | oxitriptan; tryptophan; 
mianserin; nomifensine; trazodone; 
 nefazodone; minaprine; bifemelane; 
viloxazine; oxaflozane; 
mirtazapine; bupropion; 
medifoxamine; tianeptine; 
pivagabine; venlafaxine; 
milnacipran; reboxetine; gepirone; 
duloxetine; agomelatine; 
desvenlafaxine |
| 153. | Psychostimulants, agents used for ADHD and nootropics | 154. | Centrally acting sympathomimetics |
| 155. | amphetamine; 
dexamfetamine; metamfetamine; 
methylphenidate; pemoline; 
fencamfamin; modafamil; 
armodafinil; fenozolone; 
atomoxetine; fenetylline; 
exmethylphenidate; 
lisdexamfetamine |
| 156. | Xanthine derivatives | 157. | caffeine; propentofylline |
| 158. | Other psychostimulants and nootropics | 159. | meclofenoxate; pyritinol; 
piracetam; deanol; fipexide; 
citicoline; oxiracetam; pirisudanol; 
linopirdine; nizofenone; 
aniracetam; acetylcarnitine; 
idebenone; prolintane; pipradrol; 
pramiracetam; adrafmil; 
vinpocetine; pitolisant; |
| 160. | Anti-dementia drugs | 161. | Anticholinesterases |
| 162. | tacrine; donepezil; 
rivastigmine; galantamine |
| 163. | Other anti-dementia drugs | 164. | memantine; ginkgo biloba |
| Other nervous | 165. | Parasympat | 166. | Anticholinesterases | 167. | neostigmine; pyridostigmine; |
Table 1: Psychotropic molecules

<table>
<thead>
<tr>
<th>System drugs</th>
<th>Homimetics</th>
<th>Distigmine; ambenonium;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>168. Choline esters</td>
<td>169. carbachol; bethanechol</td>
</tr>
<tr>
<td></td>
<td>170. Other parasympathomimetics</td>
<td>171. pilocarpine; choline alfoscerate; cevimeline</td>
</tr>
<tr>
<td>172. Drugs used in addictive disorders</td>
<td>173. Drugs used in nicot ine dependence</td>
<td>174. nicotine; varenicline</td>
</tr>
<tr>
<td>175. Drugs used in alcohol dependence</td>
<td>176. disulfiram; calcium carbimide; acamprosate; naltrexone; baclofene</td>
<td></td>
</tr>
<tr>
<td>177. Drugs used in opioid dependence</td>
<td>178. buprenorphine; levacetylmethad ol; lofexidine;</td>
<td></td>
</tr>
<tr>
<td>179. Antivertigo preparations</td>
<td>180. Antivertigo preparations</td>
<td>181. betahistine; cinnarizine; flunarizine; acetylleucine</td>
</tr>
<tr>
<td>182. Other nervous system drugs</td>
<td>183. Other nervous system drugs</td>
<td>184. tirilazad; riluzole; xaliproden; amifampridine; tetrabenazine; fampridine; mazindol</td>
</tr>
</tbody>
</table>

Preferably, the said psychotropic drug is selected in the group consisting of: dopaminergic, GABAergic, adrenergic, acetylcholinergic, serotoninergic, opioi dergic, adenosinergic, ionotropic, histaminergic, IMAO, Catechol-O-methyl transferase, DOPA decarboxylase, noradrenergic and glutamatergic psychotropic effectors, as well as molecules having an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

The term "effector" herein refers to any substance activating or inhibiting, directly or indirectly, one or more neuroreceptors, as well as any substance that modifies the concentration of said neurotransmitter; therefore, an effector according to the present invention can be an agonist or an antagonist of said receptors.

It is shown in the examples below that said psychotropic drug is advantageously modafnil.

As a matter of fact, the present inventors have shown that flecainide potentiates the promnesiant and/or awakening effects of modafnil (see figures 2 and 3), and that the modafinil/flecainide combination shows promising effects by reducing cataplectic-like events in mice. The precise mechanism of modafnil action has not been completely...
elucidated yet. In fact, it is known that modafinil acts on several molecular receptors, in particular on the dopamine, norepinephrine, serotonin, glutamate, GABA, orexine and histamine receptors (Ishizuka et al, 2012; Minzenberg et al, 2008). Therefore, modafinil acts as a GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and it has an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

Any compound modulating the same molecular receptors as modafinil can be advantageously associated with flecainide.

Thus, in a preferred embodiment, the psychotropic drug which is associated with flecainide acts on the very same receptors as modafinil does. The psychototropic drug associated with flecainide is therefore preferably selected in the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors. Also, it may have an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

According to a specific embodiment, the said psychotropic drug is a dopaminergic effector selected in the group consisting of: ADX-N05 (formerly "YKP10A", having the formula: (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride), amphetamine, loxapine, acepromazine, methylphenidate, pergolide, lisuride, bromocriptine, dopamine, ropinrole, apomorphine, aripiprazole, sulpiride, amisulpride, sultopride, tiapride, pimozide, risperidone, haloperidol, penfluridol, zuclopenthixol or bupropion.

According to another specific embodiment, the said psychotropic drug is a GABAergic effector selected in the group consisting of: tiagabine, topiramate, clorazepate, diazepam, clonazepam, oxazepam, lorazepam, bromazepam, lormetazepam, nitrazepam, clotiazepam, aiprozolam, estazolam, triazolam, loprazolam, etifoxin, meprobamate, zopiclone, Zolpidem, pregabaline, gabapentine, phenobarbital, felbamate and vigabatrin.

According to another specific embodiment, the said psychotropic drug is a serotoninergic effector selected in the group consisting of: chlorpromazine, trimipramine, clozapine, olanzapine, cyamemazine, flupentixol, nefopam, fluvoxamine, clomipramine, sertraline, fluoxetine, citalopram, escitalopram, paroxetine, amitriptyline, duloxetine, venlafaxine, buspirone, caripramine, zolmitriptan, sumatriptan, naratriptan, indoramine, ergotamine,
ergotamine tartrate, pizotifene, pipamperone, methysergide, pizotyline, milnacipran, viloxazine, tianeptine, hypericum and lithium.

According to another specific embodiment, the said psychotropic drug is a histaminergic effector selected in the group consisting of: acrivastine, alimemazine, antazoline, astemizole, azatadine, azelastine, brompheniramine, buclizine, carboxamine, carebastine, cetirizine, chlorcyclizine, chlorpheniramine, cinnarizine, clemastine, clemizole, clodinize, cyclizine, cyproheptadine, descarboethoxyloratidine, dexchlorpheniramine, dimenhydrinate, dimethindene, dimethothiazine, diphenhydramine, diphenylpyraline, doxylamine, ebastine, efletirizine, epinastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, loratidine, meclizine, mequitazine, methdilazine, mianserin, mizolastine, niaprazine, noberastine, norastemizole, oxatomide, oxomemazine, phenbenzamine, pheniramine, picumast, promethazine, pyrilamine, temelastine, terfenadine, tripeunenne, tripelennamine, tripeladine, ranitidine, cimetidine, famotidine, nizatidine, tiotidine, zolantidine, ciproxifan, pitolisant and ritanserin.

According to another specific embodiment, the said psychotropic drug is a hypocretin/orexin modulator selected in the group consisting of: EMPA, SB-334867, SB-674042, SB-408124, GSK1059865, almorexant, suvorexant, MK-6096, DORA-1, DORA-22, DORA-12, SB-649868, JNJ-1037049 (described in Gotter et al., 2012)).

According to another specific embodiment, the said psychotropic drug is a norepinephrinergic effector selected in the group consisting of: (R)-3-nitrobiphenyline, 2-fluoronorepinephrine, 4-NEMD, 5-fluoronorepinephrine, 6-fluoronorepinephrine, abediterol, albuterol, amibegron, amidephrine, amitraz, anisodamine, anisodine, apraclonidine, arbutamine, arformoterol, artoinolol, bambuterol, befunolol, bitolerol, brimonidine, bromoacetylalprenololmenthane, broxaterol, buphenine, cannabivarin, carbuterol, cimeterol, cirazoline, clenbuterol, denopamine, deterenol, detomidine, dexametomidine, dihydroergotamine, dipivefrine, dobutamine, dopexamine, ephedrine, epinephrine, esproquin, etafedrine, ethynorepinephrine, etilefrine, fenoterol, formoterol, guanabenz, guanfacine, guanoxabenz, hexoprenaline, higenamine, indacaterol, indanidine, isoetarine, isoprenaline, isoproterenol, isoxsuprine, labetalol, levonordefrin, levosalbutamol, lofexidine, mabuterol, medetomidine, metaraminol, methoxamine, methoxyphenamine, methylcote, midodrine, mivazerol, n-isopropyloctopamine,
naphazoline, norepinephrine, octopamine, orciprenaline, oxyfedrine, oxymetazoline, phenylephrine, phenylpropanolamine, piperoxan, pirbuterol, prenalterol, procaterol, pseudoephedrine, ractopamine, reproterol, rilmenidine, rimiterol, ritodrine, romifidine, salbutamol, salmeterol, solabegron, synephrine, talipexole, terbutaline, tetrahydrozoline, tizanidine, tolonidine, tretquinol, tulobuterol, urapidil, xamoterol, xylazine, xylometazoline, zilpaterol, and zinterol.

According to another specific embodiment, the said psychotropic drug is a glutamatergic effector selected in the group consisting of: memantine, amantadine, MK-801, ketamine, norketamine, dextromethorphan, levomerophan, dextrorphan, levorphanol, phencyclidine, PCA, CNS-1 102, remacemide, pentamidine, and 9-aminoacridine (described in Traynelis et al, 2010).

Preferably, said psychotropic drug is not flupirtine.

The potentiating effects of flecainide can be achieved by administering same to a patient, either before, at the same time, or after administration of the psychotropic drug to said patient.

Consequently, the present invention describes a method for treating a patient with psychiatric and/or neurodegenerative disorders, including the administration to said patient of a) flecainide and b) at least one psychotropic drug as mentioned above, in which said compounds a) and b) are administered simultaneously, separately or spread out over time.

Patients needing this treatment may have psychiatric, neurologic and/or neurodegenerative disorders included in the group consisting of: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic
disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics. ...), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

Excessive daytime sleepiness (EDS) occurs daily, recurring typically every 2 h, although this can vary widely. Sleepiness is exacerbated when the patient is physically inactive. The sleep episodes have several characteristics (Dauvilliers I. et al, 2007 and Boulos et al, 2010):

- They are often irresistible, despite the individual making desperate efforts to fight the urge to sleep;
- They are usually short, although their length can vary with environmental factors (eg, the duration can increase with passive activities such as watching television);
- They are frequently associated with dreaming;
- They typically restore normal wakefulness for up to several hours.

EDS characterizes several conditions or diseases: insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersonnia, recurrent hypersonmia (Kleine-Levin syndrome), circadian rhythm disorders (jet lag), disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), neurological conditions commonly associated with sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders), medical conditions commonly associated with sleepiness (respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), mood disorders, anxiety disorders, schizophrenia, or medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics. ..).
Cataplexy is characterized by a sudden drop of muscle tone triggered by emotional factors, most often by positive emotions such as laughter, repartee, pleasant surprise (e.g., seeing friends in the street or scoring a goal), or by anger, but almost never by stress, fear, or physical effort. Many neurophysiological and pharmaceutical studies indicate that cataplexy shares common neurophysiological mechanisms with REM sleep atonia (Dauvilliers I. et al, 2007).

In the case of simultaneous use, the two components of the treatment are administered to the patient simultaneously. According to this embodiment of the present invention, the two components can be packaged together, in the form of a mixture, or separately, then mixed spontaneously before being administered together to the patient. Alternatively, the two components are administered simultaneously, but separately. In particular, the routes of administration of the two components may be different. The administration can also be performed at different sites. In another embodiment, the two components are administered sequentially or spaced apart over time, for example in the same day or at an interval ranging from several minutes to several days.

Since flecainide potentiates the effects of psychotropic drugs, it can advantageously be used for reducing the doses of said psychotropic drug, thereby limiting the adverse effects of said psychotropic drug, and/or reducing the risks of failure and withdrawal.

The effective equivalent dose of a psychotropic drug, i.e., the psychotropic drug dose that, when administered in combination with flecainide, induces a physiological effect or a pharmacological signature similar or identical to that of the psychotropic drug alone administered at the active pharmacological dose, can be determined by the methods disclosed in WO2010/029131 and US 201 1/172188.

According to another aspect, the present invention pertains to a composition, especially a pharmaceutical composition, comprising flecainide and at least one psychotropic drug. This composition is preferably formulated for patients with psychiatric and/or neurodegenerative disorders, as disclosed above. In addition to flecainide and to said psychotropic drug, the composition can comprise any pharmaceutical vehicle, stabilizer, adjuvant and the like as frequently used in the art.
Examples of pharmaceutically acceptable vehicles include, but are not limited to: water; aqueous vehicles such as, but not limited to, sodium chloride solution, Ringer's solution, dextrose solution, dextrose and sodium chloride solution, and lactated Ringer's solution; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and nonaqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

According to a preferred embodiment, this composition is formulated for oral administration (including buccal cavity or sublingually). Other interesting formulations include formulations for intraperitoneal (i.p.), intravenous (i.v.), subcutaneous (s.c), intramuscular (i.m.), transcutaneous, transdermal, intrathecal and intracranial administrations. Still other formulations include epidural, submucosal, intranasal, ocular cul-de-sac and rectal routes of administration, as well as administration by pulmonary inhalation.

A variety of administration means, including but not limited to capsules, tablets, syrups, creams and ointments, suppositories, patches or any reservoir capable of containing and dispensing flecainide and the psychotropic drug, can be used for formulating the above-described compositions.

In the compositions according to the invention, the psychotropic drug is as described above.

In a preferred embodiment, said psychotropic drug is used for treating narcolepsy and is therefore selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafnil and armodafinil.

In a preferred embodiment, the composition of the invention contains between 1 to 1000 mg, preferably 5 to 800 mg of the psychotropic drug, depending of its nature. A preferred posology would be to administer to the patient between 1 to 1000 mg/day, more preferably between 5 to 800 mg/day of the psychotropic drug.
According to another preferred embodiment, the composition of the invention contains between 1 to 200, preferably 1 to 100 mg of flecainide. A preferred posology would be to administer to the patient between 1 to 200, preferably 1 to 100 mg/day of flecainide.

More preferably, said flecainide is the R enantiomer disclosed on figure 5A.

In a more preferred embodiment, flecainide is associated with the psychotropic drug modafnil.

By "modafnil" is herein meant the 2-[(diphenylmethyl) sulfonyl] acetamide (Provigil, see figure 5C), as well as its precursors or prodrugs such as adrafmil (Dubey et al, 2009) which can be metabolized in the human body and its active derivatives. More precisely, the term "Modafnil" herein designates any form of modafnil (racemate, R-modafnil, S-modafnil, etc.), as well as its precursors which can be metabolized in the human body and its derivatives. Figure 5 shows the formulas of R-Modafnil (Fig. 5C) and S-Modafnil (Fig. 5D).

Modafnil is an analeptic drug prescribed essentially for the treatment of narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea. Besides these wake-promoting properties, modafnil also improves working memory and episodic memory, and other processes dependent on prefrontal cortex and cognitive control (Minzenberg MJ et al, 2008).

The present inventors have shown that, surprisingly, flecainide strongly potentiates in vivo the waking effects of Modafnil, whereas it has no effect on wake duration on its own (example 2). Moreover, flecainide strongly potentiates in vivo the cognitive activity of Modafnil, whereas it has no promnesiant effect on its own (example 3). This synergistic activity could be explained by the fact that flecainide strongly extends the duration of Modafnil treatment (example 4). On the other hand, the present inventors herein describes that the flecainide / modafnil combination has a synergistic effect on cataplectic-like phenotype in narcoleptic mice (example 5) and is all the more surprising than either flecainide or modafnil has no effect on this phenotype (figure 6B). In a preferred embodiment, the present invention thus pertains to flecainide, for use for potentiating the promnesiant and/or awakening effects of modafnil, and/or for improving its safety, and/or for increasing the duration of action of modafnil in patients in need thereof, especially in
patients suffering from: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, antipsychotics, ..), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia, which have been proposed to be treated by modafnil.

In a more preferred embodiment, the present invention specifically pertains to flecainide, for use for potentiating the awakening effects of modafnil, and/or for improving its safety, and/or for increasing the duration of action of modafnil in patients suffering from: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-
psychotics..), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia, for which modafinil has been proposed or authorized.

In a preferred embodiment, the present invention specifically pertains to flecainide, for use for potentiating the awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients suffering from excessive daytime sleepiness (EDS).

In another preferred embodiment, the present invention relates to flecainide, for use for potentiating the awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients suffering from conditions or diseases involving EDS, that are for example: insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, recurrent hypersomnia (Kleine-Levin syndrome), circadian rhythm disorders (jet lag), disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders and sleepiness), restless legs syndrome (RLS) and Periodic Limb Movement Disorders (PLMD), neurological conditions commonly associated with sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders), medical conditions commonly associated with sleepiness (respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), mood disorders, anxiety disorders, schizophrenia, or medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics...).

In another preferred embodiment, the present invention relates to a modafinil/flecainide combination product, for use for treating cataplexy in narcoleptic patients.

It is to be noted that the potentiation of the effects of modafinil by flecainide enables a reduction of the dose of modafinil, and hence a reduction of its side-effects. As a consequence, some applications of modafinil, for which this drug was not approved because of its side-effects and possible risks associated thereto, can now be envisioned,
such as its use as a performance-enhancing and/or brain-boosting agent. According to a particular embodiment, the present invention thus pertains to a performance-enhancing product comprising flecainide and modafinil.

In another preferred embodiment, the present invention specifically pertains to the use of flecainide and modafinil for enhancing the memory of healthy subjects and/or to maintain them awake for long-lasting periods of time and/or to treat cataplexy in narcoleptic patients. These subjects can be for example individuals that need to memorize a lot of information and/or to remain awake for long lasting periods. In a preferred embodiment, said subjects are humans (e.g., security agents, students, etc.).

In a particular embodiment, the present invention also relates to a composition comprising flecainide and modafinil, which can advantageously be used for treating diseases and conditions including but not limited to excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, jet-lag, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia. In particular, this composition can be used for treating cataplexy in narcoleptic patients.

This composition can also be used for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time. Typical periods of time are for example 6 hours, preferably 12 hours.

The present invention moreover relates specifically to the use of flecainide and modafinil in the preparation of a medicament that is intended to be used for treating diseases and conditions such as excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.
In a preferred embodiment, the present invention relates to the use of flecainide and modafmil in the preparation of a medicament that is intended to be used for treating cataplexy in narcoleptic patients.

In addition to modafmil and flecainide, the composition / medicament of the invention can comprise other agents such as vitamin C, vitamin B6, magnesium, L-arginine, L-glutamine, L-citrulline, taurine, caffeine, etc. According to a particular embodiment, this product can be sold over-the-counter. It can be formulated, for example, as an OTC medicine or as a food supplement.

In a preferred embodiment, the composition of the invention contains between 1 to 1000 mg, preferably between 5 to 800 mg, and more preferably between 5 to 600 mg of the modafmil. According to another preferred embodiment, the composition of the invention is formulated so that 5 to 800, preferably 5 to 600 mg/day of modafmil are administered to a patient in need thereof, in one, two or more takings.

According to another preferred embodiment, the composition of the invention contains between 1 to 200, preferably 1 to 100 mg of flecainide. According to another preferred embodiment, the composition of the invention is formulated so that 1 to 200, preferably 1 to 100 mg/day of flecainide are administered to a patient in need thereof, in one, two or more takings. In a more preferred embodiment, said flecainide is the R enantiomer disclosed on figure 5A.

In a final aspect, the present invention relates to a combination product comprising flecainide and modafmil, for simultaneous, separated or staggered use for preventing and/or treating excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, jet-lag, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia. This combination product is preferably used for preventing and/or treating cataplexy in narcoleptic patients.
Other characteristics of the invention will also become apparent in the course of the description which follows of the biological assays which have been performed in the framework of the invention and which provide it with the required experimental support, without limiting its scope.

Legends to the figures

Figure 1: Inhibition of the human connexins functionality by flecainide. Rin-Cx26 cells, Rin-Cx30 cells, Rin-Cx32 cells, Rin-CX40 cells and Rin-Cx43 cells are cultured in the presence of flecainide (280µM), mefloquine (10 µM) and MFA (100 µM) for 4 hours. The transfer of fluorochrome by gap junctions (composed of connexins) is evaluated by flow cytometry (1A and 1B). Viability of the cells treated with flecainide is shown on figure 1B.

Figure 2: Efficiency of flecainide for potentiating the awakening effect of modafinil. Mice (n = 8 per batch) were orally treated by either modafinil (32 mg/kg) or modafinil (32mg/kg) and flecainide (1mg/kg) (figure 2A) or flecainide alone (1mg/kg) (figure 2B) and replaced in their home cage. The wake duration was measured using polygraphic analyses.

Figure 3: Efficacy of flecainide for potentiating the promnesiant effect of modafinil. Mice (n = 6 to 23 per batch) are tested in the T-maze. They were intraperitoneally treated by either modafinil (64 mg/kg or 128mg/kg) or modafinil (64mg/kg) and flecainide (lmg/kg) or flecainide alone (lmg/kg). The graphic represents the percentage of alternation after 6 trials, 50% corresponding to a random alternation.

Figure 4: Efficacy of flecainide for potentiating the locomotor effect of modafinil. Mice (n=8 per batch) were orally treated by either modafinil (64 mg/kg) or modafinil (64mg/kg) and flecainide (lmg/kg) or flecainide alone (lmg/kg) and replaced in their home cage. The locomotor activity was measured using videotracking device.

Figure 5: Molecular structure of A. R-flecainide; B. S-flecainide; C. R-Modafnil, D. S-Modafnil.
**Figure 6**: Number of episodes of OREM/DREM phases in narcoleptic mice (Ox-/-) treated by modafinil/flecainide (A) or flecainide alone (B). Oral treatment of Ox-/- male mice with modafinil 64 mg/kg with flecainide 1 mg/kg was compared to Modafinil 64 mg/kg and vehicle. **: p<0.01 ; ***: p<0.005, Two-Way ANOVA. (B) Oral treatment of Ox-/- male mice with flecainide 1 mg/kg was compared to vehicle.

**Figure 7**: Number of episodes of OREM/DREM phases in narcoleptic mice (Ox-/-) treated by the combination between modafinil and one of the two enantiomers of flecainide (R-flecainide and S-flecainide). Oral treatment with modafinil 64 mg/kg with R-flecainide 1 mg/kg or S-flecainide 1 mg/kg was compared to vehicle.

**EXAMPLES**

**Example 1: Effect of Flecainide on gap junctions**

1.1. Materials and methods

**Cell culture**

The rat insulinoma RIN cell line, deficient in GJIC (del Corso et al, 2006), was grown in OptiMem medium, supplemented with 10% fetal calf serum. GJB6 (Cx30), GJB1 (Cx32), GJB2 (Cx26), GJA5 (Cx40) and GJA1 (Cx43) open reading frames were amplified from human cDNA. The open reading frames were cloned in pcDNA3.1/V5-His-TOPO (Invitrogen). Cells were transfected using Lipofectamine and further selected using geneticin.

**Dye transfer experiments**

Cells were seeded and loaded with two fluorochromes, calcein acetoxymethyl ester, a gap junction permeable dye, and Vybrant Dil, a membrane lipophilic dye. The next day, cells were dissociated and incubated for four hours in presence of previously seeded non-loaded cells and in the presence of flecainide racemate 70, 140 or 280 µM, mefloquine 10 µM or meclofenamic acid (MFA) 100 µM. Flow cytometry was conducted on a FACScan.
Inhibition was quantified as the relative number of receiver cells that gained fluorescence to the total number of receiver cells (non GJ-mediated dye transfer was then substracted to these ratio based on connexin non-expressing RIN cells, defined at background dye transfer ratio). This ratio of cellular coupling was then normalized, after each treatment, on the vehicle one.

Toxicity analysis

Twenty thousand RIN were seeded in 100 µl of culture medium in 96-wells plates. After 48h culture, cells were treated for 4 hours with previously identified chemical compounds at several concentrations. Cells were rinsed in PBS and grown 24h in fresh medium. Cell viability was measured by using WST-1 (Roche).

1.2. Experimental results

Cellular models were validated by using two classical inhibitors described in litterature, meclofenamic acid (MFA) (Dhein, 2004) (100 µM) and mefloquine (Cruikshank et al, 2004) (10 µM). Results are shown on figure 1A. Flecaïnide is as efficient in blocking connexin as the other anti-connexin agents.

Cell viability tests (using WST-1, dotted curve on Figure IB) after one day of treatment, indicate that flecaïnide has no cell toxicity at the dose inhibiting cerebral connexins.

In addition, flecaïnide inhibits all the tested isoforms of cerebral connexin using dye-transfer cell-parachute assay (Cx30, Cx32, Cx26, Cx40, Cx43) (it is estimated that a more than a significant 10% reduction in gap junction cellular is considered as physiologically relevant). In addition, higher inhibition levels are reached for glial connexins Cx26, Cx30 and Cx43.

**Example 2: Flecaïnide potentiates the waking effects of Modafinil**

Preclinical and clinical data indicated that modafinil modifies sleep-cycle rhythm and promotes wake phases (Lin et al, 2008). Here we tested in rodents whether such activity was potentiated by flecaïnide after oral challenge with modafinil, using polysomnographic analysis on implanted mice. Using a sub-efficient dosage of modafinil (32 mg/kg), the
inventors demonstrated a new feature of the combination of modafinil and flecainide since it significantly increases the total duration of wake episodes.

2.1. Materials and Methods

Wild-type C57Bl/6 male mice (n=9/groups) were implanted with EEG/EMG/EOG electrodes for polysomnographic analyses. After a two-week recovery period, mice were orally treated with vehicle, Modafnil 32 mg/kg and Modafnil 32 mg/kg + flecainide racemate 1 mg/kg and wake periods were quantified using Spike2 scripts. Here the inventors represented the duration of wake during the first three hours (after a one-hour period post-administration). **: p<0,01 in a One-Way ANOVA analysis.

2.2. Results

Modafmil is a molecule that promotes wakefulness in humans and mice, increasing in mice their activity in a dose-dependent manner (Simon et al, 1994). The activity of mice treated with modafmil at 32 mg/kg was compared with that of mice treated with the combination modafmil 32 mg/kg + flecainide 1 mg/kg or vehicle.

Figure 2A shows that flecainide significantly increases the waking effects of modafmil. Figure 2B shows that this effect is not mediated by flecainide alone.

Thus, flecainide significantly potentiates modafmil waking activity in wild type mice, while being devoid of own effect on wake duration.

**Exemple 3: Flecainide significantly enhances modafnil cognitive activity**

Modafmil induces a cognitive enhancing effect (Beracochea et al, 2003), such property can be assessed using the alternating sequential test, a widely used apparatus to assess spatial working memory in mice (Beracochea & Jaffard, 1987). Spontaneous alternation is the innate tendency of rodents to alternate their choices to enter into the compartments of arrival of a T-maze device, over successive trials. To alternate during a given trial N, the animal must remember the choice made selectively in test N-1, and the response in alternating is performance measure. Acute administration of modafinil before entering the maze, can improve the performance of mice in this test (Beracochea et al, 2001). The
inventors’ results showed that flecainide significantly potentiates the promnesiant effect of a subefficient dose of modafnil, while flecainide alone is devoid of any own promnesiant effect.

3.1. Materials and methods

The alternating sequential test is widely used to assess spatial working memory in mice (Beracochea & Jaffard, 1987). Spontaneous alternation is the innate tendency of rodents to alternate their choices to entry into the compartments of arrival of a T-maze device, over successive trials. To alternate during a given trial N, the animal must remember the choice made selectively in test N-1, so the decline in alternating will reflect the phenomenon of oblivion. The response in alternating is performance measure. Sequential alternating assesses more specifically the sensitivity to interference, a major factor in oblivion.

The experiment takes place in a T-maze (50 cm x 10 cm x 25 cm). All the subjects were given 7 successive trials separated by a 120-s intertrial interval. To begin a trial, the mouse was placed in the start box for 120 s before the door to the stem was opened. When the subject entered one of the goal arms, the door to that arm was closed. The chosen arm and the time that elapsed between opening the door and the arrival to the end of the chosen arm (task achievement time) were registered. Following a 30-s confinement period (fixed and invariant) in the chosen arm, the animal was removed and placed in the start box for a new trial. Between each test, the unit is cleaned with a cloth soaked in water and alcohol to avoid olfactory detection. The index memory is represented by the average of alternating percentage (number of alternation choices / total number of tests X 100). (n=6 to 23 for each group). Mice were intraperitoneally treated by either modafnil (64 mg/kg or 128mg/kg) or modafnil (64mg/kg) and flecainide racemate (1mg/kg) or flecainide racemate alone (1mg/kg) or vehicle.

# p<0,05 in one sample t-test vs random 50% alternance ; * p<0,05 One way ANOVA followed by Tukey's multiple comparison vs modafmil group.
3.2 Results

The T-maze is a device for assessing working memory in mice. Acute administration of modafinil before entering the maze, can improve the performance of mice in this test (Beracochea et al, 2001).

The validity of the test was performed by comparing the responses of mice intraperitoneally treated with an effective dose of modafinil alone (128 mg/kg), a dose of flecainide alone (1 mg/kg) and a sub-effective dose of modafinil (64 mg/kg) with or without flecainide alone (1 mg/kg). The results are shown in Figure 3.

These results show that flecainide significantly potentiates modafinil promnesiant activity, while flecainide alone shows no own cognitive effect.

**Exemple 4: Flecainide significantly prolongs modafinil activity**

Modafinil is a molecule that promotes wakefulness in humans and mice, increasing in mice their activity in a dose-dependent manner (Simon et al, 1994). The inventors' results showed that flecainide significantly potentiates the locomotor effect of a subefficient dose of modafinil, while flecainide alone is devoid of any own locomotor effect in rodents.

4.1. Materials and methods

Mice (n=8 per batch) were orally treated by either modafinil (64 mg/kg) or modafinil (64mg/kg) and flecainide racemate (1mg/kg) or flecainide racemate alone (1mg/kg) or vehicle and replaced in their home cage. Locomotor activity is evaluated by video tracking. Videos have been analyzed using Ethovision XT software (Noldus®).*: p<0,01 in a Two-Way ANOVA analysis

4.2. Results

The activity of mice treated with modafinil at 64 mg/kg was compared with that of mice treated with the combination modafinil 64 mg/kg + flecainide 1 mg/kg. Figure 4 shows that flecainide significantly increases the duration of effect of modafinil on the activity of mice.
To conclude, the above results show that Flecainide significantly inhibits the functionality of gap junctions, without inducing cellular toxicity. In addition, this compound potentiates the efficacy and duration of effect of modafnil, notably in its promnesiant and awakening side.

Exemple 5: Modafinil/Flecainide combination has a surprising efficient profile on DREM cataplectic-like phenotype in narcoleptic mice.

5.1. Material and methods

Animals

Prepro-orexin knockout (KO) mice were offspring of the mouse strain generated by Chemelli et al. [1999] and kept on C57BL/6J genomic background. After backcrossing male orexin-/− mice and female wild-type (WT) mice for nine generations, the obtained orexin+/− mice were crossed to produce heterozygote and homozygote WT and KO littermates. To determine their genotypes with respect to orexin gene, tail biopsies were performed at the age of 4 weeks for DNA detection using PCR.

Surgery

At the age of 12 weeks and with a body weight of 30±2 g, mice used for EEG and sleep-wake studies were chronically implanted, under deep gas anesthesia using isoflurane (2%, 200 ml/min) and a TEM anesthesia system (Bordeaux, France), with six cortical electrodes (gold-plated tinned copper wire, 0 = 0.4 mm, Filotex, Draveil, France) and three muscle electrodes (fluorcarbon-coated gold-plated stainless steel wire, 0 = 0.03 mm, Cooner Wire Chatworth, CA, U.S.A.) to record the electroencephalogram (EEG) and electromyogram (EMG) and to monitor the sleep-wake cycle. All electrodes were previously soldered to a multi-channel electrical connector and each was separately insulated with a covering of heat-shrinkable polyolefin/polyester tubing. Cortical electrodes were inserted into the dura through 3 pairs of holes made in the skull, located
respectively in the frontal (1 mm lateral and anterior to the bregma), parietal (1 mm lateral to the midline at the midpoint between the bregma and lambda), and occipital (2 mm lateral to the midline and 1 mm anterior to the lambda) cortex. Muscle electrodes were inserted into the neck muscles. Finally, the electrode assembly was anchored and fixed to the skull with Super-Bond (Sun Medical Co., Shiga, Japan) and dental cement. This implantation allows stable and long-lasting polygraphic recordings [Parmentier et al, 2002].

**Polygraphic recording in the mouse and data acquisition and analysis**

After surgery, the animals were housed individually, placed in an insulated sound-proof recording room maintained at an ambient temperature of 23±1 °C and on a 12 h light/dark cycle (lights-on at 7 a.m.). After a 7-day recovery period, mice were habituated to the recording cable for 7 days before polygraphic recordings were started. Direct REM sleep onset (DREMs) episodes, also called narcoleptic episodes or sleep onset REM periods by some authors [Chemelli et al, 1999; Mignot et al, 2005; Fujiki et al, 2006], were defined as the occurrence of REM sleep directly from wake, namely a REM episode that follows directly a wake episode lasting more than 60 s without being preceded by any cortical slow activity of more that 5 s during the 60 s.

**Drug administration and experimental procedures in the mouse**

After recovery from the surgery and habituation to the recording cables, each mouse was subjected to a recording session of two continuous days, beginning at 7 a.m. Administrations were performed at 6:45 p.m. just before lights-off (7:00 p.m.), since orexin-/ mice display narcoleptic attacks only during lights-off phase [Chemelli et al, 1999]. The order of administration was randomized. Polygraphic recordings were made immediately after administration and were maintained during the whole lights-off period (12 h). Two administrations were separated by a period of 7 days (washout). Mice (n=8 per batch) were orally treated by either modafnil (64 mg/kg) or modafinil (64mg/kg) and flecainide racemate (lmg/kg) or flecainide racemate alone (lmg/kg) or vehicle.

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Orexins (also known as hypocretins) are two hypothalamic neuropetides identified in 1998 [Sakurai et al, 1998; De Lecea L. et al, 1998]. Neurons containing orexins have been identified in the hypothalamic dorsolateral and peri-fornical areas, these neurons play a key role in behavioral arousal. A large body of evidence indicates that an orexin deficiency is responsible for the pathogenesis of human and animal narcolepsy [Lin et al, 1999; Chemelli et al, 1999]. It has been recently shown that the most major phenotypes of orexin KO mice are a behavior/motor deficit during waking and the occurrence, during the dark phase, of episodes of sleep onset REM (DREM, as known as SOREM) - defined on EEG, EMG and video recordings as sudden onset of paradoxical sleep directly from wakefulness [Anaclet et al, 2009]. Thus SOREM/DREM constitutes a main phenotype of murine narcolepsy which is frequently seen in narcoleptic patients [Lin et al, 2001]. Using this model, it was shown that modafinil allows DREM episodes to persist [Lin et al, 2008], a situation similar to that in the clinic in which modafinil improves excessive daytime sleepiness without clear effect in cataplexy.

Moreover, as disclosed on figure 6B, flecainide racemate (alone), at 1 mg/kg dose, has no effect on DREM cataplectic-like phenotype in narcoleptic Ox-/− mice.

However, and importantly, the results disclosed on figure 6A show that modafinil/flecainide combination decreases the occurrence of DREM episode.

Hence, flecainide and modafinil do not have any significant effect on a DREM cataplectic-like phenotype when used alone, whereas their combination importantly decreases the DREM cataplectic-like phenotype.

These results highlight the synergy existing between flecainide and modafinil, said synergy being due to the potentiation of the modafinil efficiency by flecainide, since no effect is seen with either modafinil or flecainide alone in narcoleptic mice.
Exemple 6: Modafinil/R-flecainide is surprisingly more efficient than Modafinil/S-flecainide on DREM cataplectic-like phenotype in narcoleptic mice.

The same materials and methods than in example 5 were used, except that the flecainide racemate has been replaced by the R-flecainide enantiomer.

As disclosed on figure 7, R-flecainide enantiomer combined with modafinil is more efficient on DREM cataplectic-like phenotype in narcoleptic Ox-/- mice than the S-flecainide enantiomer combined with modafinil.
REFERENCES


CLAIMS

1. A therapeutic composition comprising flecainide and at least one psychotropic drug, wherein said psychotropic drug is modafnil.

2. The therapeutic composition according to claim 1, for use for treating excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics…), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

3. The therapeutic composition of claims 1 or 2, for use for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time.

4. The therapeutic composition of claims 1 or 2, for use for treating cataplexy in narcoleptic patients.
5. The therapeutic composition of any one of claims 1 to 4, wherein said flecainide is the R enantiomer of formula:

![Chemical structure](image)

6. A combination product comprising flecainide and modafnil, for simultaneous, separated or staggered use for preventing and/or treating excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics...), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

7. The combination product of claim 6, for use for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time.

8. The combination product of claim 6, for use for treating cataplexy in narcoleptic patients.
9. The combination product of any one of claims 6 to 8, wherein said flecainide is the R enantiomer of formula:

![Chemical Structure]

10. *In vitro* use of flecainide as an anti-connexin agent.

11. *In vitro* use of claim 10, wherein said flecainide is the R enantiomer of formula:

![Chemical Structure]

12. *In vitro* use according to claim 10 or 11, for blocking one or more connexin molecule selected from the group consisting of: Connexin 23, Connexin 25, Connexin 26, Connexin 30, Connexin 30.2, Connexin 30.3, Connexin 31, Connexin 31.1, Connexin 31.9, Connexin 32, Connexin 36, Connexin 37, Connexin 40, Connexin 40.1, Connexin 43, Connexin 45, Connexin 46, Connexin 47, Connexin 50, Connexin 59, and Connexin 62.

13. *In vitro* use according to claim 10 or 11, for blocking one or more connexin molecule selected from the group consisting of: connexin 26, connexin 30, connexin 30.2, connexin 32, connexin 36, connexin 37, connexin 40, connexin 43, connexin 45, connexin 46 and connexin 47.
14. *In vitro* use according to claim 10 or 11, for blocking one or more connexin molecule selected from the group consisting of: connexin Cx40, connexin Cx26, connexin 30, connexin 32, and connexin 43.

15. Flecainide for use as an anti-connexin agent, for potentiating the effects of a psychotropic drug, preferably for increasing the efficacy and/or safety and/or the duration of action of a psychotropic drug.

16. Flecainide for use according to claim 15, wherein said psychotropic drug is selected from the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and those having an effect on the hypocretin/orexin system.

17. Flecainide for use according to claim 15 or 16, wherein said psychotropic drug is selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate monohydrochloride, modafnil and armodafnil.

18. Flecainide for use according to any of claims 15 to 17, for potentiating the effects, preferably the promnesiant effect and/or the awakening effect, of a psychotropic drug selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate monohydrochloride, modafnil and armodafnil.

19. Flecainide for use according to any of claims 15 to 18, for increasing the efficacy and/or the duration of action of a psychotropic drug selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate monohydrochloride, modafnil and armodafnil.

20. Flecainide for use according to any of claims 15 to 19, wherein said psychotropic drug is modafnil.
21. Flecainide for use according to any of claims 15 to 20, wherein said flecainide is the R enantiomer of formula:

```
F3C  
\ |  
|   
\|   
H N   H  
|   
\|   
C H   O 
```

5 22. A therapeutic composition comprising flecainide and at least one psychotropic drug, wherein said psychotropic drug is not flupirtine.

23. The therapeutic composition according to claim 22, wherein said psychotropic drug is selected from the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and those having an effect on the hypocretin/orexin system.

24. The therapeutic composition according to any of claims 22 or 23, wherein said psychotropic drug is a psychotropic drug selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafinil and armodafmil, preferably modafmil.

25. The therapeutic composition according to any of claims 22 or 23, wherein said flecainide is the R enantiomer of formula:

```
F3C  
\ |  
|   
\|   
H N   H  
|   
\|   
C H   O 
```
26. Flecainide for use as an anti-connexin agent, for treating a disorder selected from the group consisting of: wounds, migraines, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia.

27. Flecainide for use according to claim 26, wherein said flecainide is the R enantiomer of formula:
Figure 1

A

- Flecaïnide 280 µM
- Méfloquine 10 µM
- Méclofenamic Acid 100 µM

B

Viability (%) or G.J functionality (%) vs. Flecaïnide (µM)
Figure 3

The figure shows a bar chart with alternance score on the y-axis and different treatments on the x-axis. The treatments include Vehicle, Flecaïnide 1, Modafinil 64, Modafinil 64 + Flecaïnide 1, and Modafinil 128. The chart indicates significant differences (*) and trends (#) between the treatments.
Figure 5

A

B

C
Figure 5 (continued)

\[
\begin{align*}
\text{D}
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\]
Figure 6

A

- Modafinil 64 + Flecainide 1
- Modafinil 64
- Vehicle

Cumulative number of DREM vs. Hours post-treatment

B

- Flecainide 1
- Vehicle

Cumulative number of DREM vs. Hours post-treatment
Figure 7

Two-way ANOVA, repeated measures by both factors

*p<0.05 vs Vehicule
#p<0.05 vs Modafinil 64
1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
   a. (means)
      □ on paper
      □ in electronic form
   b. (time)
      □ in the international application as filed
      □ together with the international application in electronic form
      □ subsequently to this Authority for the purpose of search

2. □ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 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:

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 No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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.:

1-14, 20(completely) ; 15-19, 21-25(partially)

Remark on Protest

□ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/435 A61P25/00 A61P25/06 A61P25/08 A61P25/26
A61P25/28 A61P35/00...

B. FIELDS SEARCHED

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 practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

claims 2, 4

claims 27, 31

* 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 application or patent 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

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search 16 September 2014

Date of mailing of the international search report 08/01/2015

Name and mailing address of the ISA/
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NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer
Bittner, Ulf
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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 20 (completely); 15-19, 21-25 (partially) 
   A) a composition comprising flecainide and modafinil 
   B) Flecainide as an anti-connexin agent for in vitro use 

2. claims: 15-19, 21-25 (partially) 
   The use of flecainide to potentiate the effects of a psychotropic drug 

3. claims: 26, 27 
   Flecainide for potentiating the effect of psychotropic drugs and for the treatment of psychiatric disorders as defined in claim 26.