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(54) Title: COMBINATIONS COMPRISING ANTI-EPILEPTIC DRUGS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

(57) Abstract: This invention relates to combinations comprising two anti-epileptics, pharmaceutical compositions comprising such combinations, and the use of such combinations for the preparation of a medicament for the treatment of neurological disorders, esp. epilepsy.

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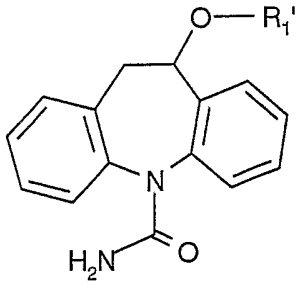
Combinations Comprising Anti-epileptic Drugs for the Treatment of Neurological Disorders

The present invention relates to combinations suitable for the treatment of neurological disorders, in particular epilepsy. Epilepsy is characterized by abnormal discharges of cerebral neurons and typically manifested as various types of seizures. 20 to 30 % of epilepsy patients are refractory to current therapy.

Surprisingly, it has been found that the effect of a combination which comprises two anti-epileptic drugs selected from the list consisting of barbiturates and derivatives thereof, benzodiazepines, carboxamides, hydantoins, succinimides, valproic acid and other fatty acid derivates, AMPA antagonists and other anti-epileptic drugs is greater than the additive effect of the combined anti-epileptic drugs. Furthermore, the combinations disclosed herein can be used to treat epilepsy which is refractory to monotherapy employing one of the combinations alone.

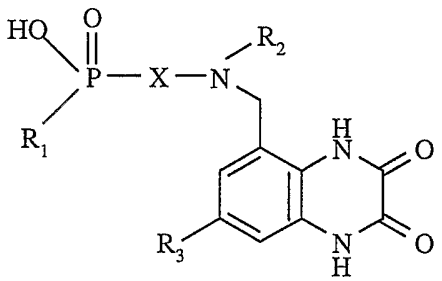
Hence, the invention relates to a combination, such as a combined preparation or pharmaceutical composition, which comprises two anti-epileptics selected from the list consisting of barbiturates and derivatives thereof, benzodiazepines, carboxamides, hydantoins, succinimides, valproic acid and other fatty acid derivates, AMPA antagonists and other anti-epileptic drugs, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

The term "barbiturates and derivatives thereof" as used herein includes, but is not limited to phenobarbital, pentobarbital, mepobarbital and primidon. The term "benzodiazepines" as used herein includes, but is not limited to clonazepam, diazepam and lorazepam. The term "carboxamides" as used herein includes, but is not limited to carbamazepine, oxcarbazepine, 10-hydroxy-10,11-dihydrocarbamazepine and the compounds of formula II



(II)

wherein R_1' represents C_1-C_3alkyl carbonyl. The term "hydantoins" as used herein includes, but is not limited to phenytoin. The term "succinimides" as used herein includes, but is not limited to ethosuximide, phensuximide and mesuximide. The term "valproic acid and other fatty acid derivates" as used herein includes, but is not limited to valproic acid sodium salt, tiagabine hydrochloride monohydrate and vigrabatrine. The term "other anti-epileptic drugs" as used herein includes, but is not limited to levetiracetam, lamotrigine, gabapentin, sultiam, felbamate, the 1,2,3-1H-triazoles disclosed in EP 114 347, esp. rufinamide [1-(2,6-difluoro-benzyl)-1H-[1,2,3]triazole-4-carboxylic acid amide] and the 2-aryl-8-oxodihydropurines disclosed in WO99/28320. The term "AMPA antagonists" as used herein includes, but is not limited to the quinoxalinedione aminoalkylphosphonates of formula I



I

wherein

R_1 is hydroxy or (C_{1-4})alkyl,

R_2 is (C_{1-4})alkyl,

R_3 is hydrogen, (C_{1-4}) alkyl, fluorine, chlorine, bromine, trifluoromethyl, cyano or nitro, and

X is (C_{1-6})alkylene, (C_{1-6})alkylidene, (C_{1-6})alkylene(C_{3-6})cycloalkylene or (C_{1-6})alkylene-(C_{3-6})cycloalkylidene, wherein the radicals and symbols have the meanings as defined in WO 98/17672; CX 691, EGIS 8332 (7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carbonitrile), GYKI 47261 (4-(8-chloro-2-methyl-11H-imidazo[1,2-c][2,3]benzodiazepin-6-yl)benzenamine), Irampanel (BIIR 561; N,N-dimethyl-2-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)phenoxy]ethanamine), KRP 199 (7-[4-[[[[(4-

carboxyphenyl)amino]carbonyl]oxy]methyl]-1H-imidazol-1-yl]-3,4-dihydro-3-oxo-6-(trifluoromethyl)-2-quinoxalinecarboxylic acid), NS 1209 (2-[[[5-[4-[(dimethylamino)-sulfonyl]phenyl]-1,2,6,7,8,9-hexahydro-8-methyl-2-oxo -3H-pyrrolo[3,2-h]isoquinolin-3-ylidene]amino]oxy]-4-hydroxybutanoic acid monosodium salt, e.g. prepared as described in WO 98/14447), topiramate (TOPAMAX, 2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate, preparation, e.g. as described in US 535475) and talampanel ((R)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzo-diazepine, preparation, e.g. as described in EP 492485).

Phenobarbital, can be administered, e.g., in the form as marketed, e.g. under the trademark Luminal™. Primidon can be administered, e.g., in the form as marketed, e.g. under the trademark Mylepsinum™. Clonazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Antelepsin™. Diazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Diazepam Desitin™. Lorazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Tavor™. Carbamazepine can be administered, e.g., in the form as marketed, e.g. under the trademark Tegretal™ or Tegretol™. Oxcarbazepine can be administered, e.g., in the form as marketed, e.g. under the trademark Trileptal™. Oxcarbazepine is well known from the literature [see for example Schuetz H. et al., Xenobiotica (GB), 16(8), 769-778 (1986)]. The preparation of the compound of formula II wherein R_1' is C_1-C_3alkyl carbonyl and its pharmaceutically acceptable salts is described, e.g., in US 5,753,646. 10-Hydroxy-10,11-dihydro-carbamazepine can be prepared as disclosed in US 3,637,661. 10-Hydroxy-10,11-dihydrocarbamazepine may be administered, e.g., in the form as described in US 6,316,417. Phenytoin can be administered, e.g., in the form as marketed, e.g. under the trademark Epanutin™. Ethosuximide can be administered, e.g., in the form as marketed, e.g. under the trademark Suxinutin™. Mesuximide can be administered, e.g., in the form as marketed, e.g. under the trademark Petinutin™. Valproic acid sodium salt can be administered, e.g., in the form as marketed, e.g. under the trademark Leptilan™. Tiagabine hydrochloride monohydrate can be administered, e.g., in the form as marketed, e.g. under the trademark Gabitril™. Vigabatrine can be administered, e.g., in the form as marketed, e.g. under the trademark Sabril™. Levetiracetam can be administered, e.g., in the form as marketed, e.g. under the trademark Keppra™. Lamotrigine can be administered, e.g., in the form as marketed, e.g. under the trademark Lamictal™. Gabapentin can be administered, e.g., in the form as marketed, e.g. under the trademark Neurontin™. Sultiam can be administered, e.g.,

in the form as marketed, e.g. under the trademark Ospolot™. Felbamate can be administered, e.g., in the form as marketed, e.g. under the trademark Taloxa™. Topiramate can be administered, e.g., in the form as marketed, e.g. under the trademark Topamax™. The 1,2,3-1H-triazoles disclosed in EP 114 347 may be administered, e.g., in the form as described in US 6,455,556. The 2-aryl-8-oxodihydropurines disclosed in WO99/28320 may be administered, e.g., in the form as described in WO99/28320. The compounds of formula I as well as their production process and pharmaceutical compositions thereof are known e.g. from WO 98/17672.

The structure of the active ingredients identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active ingredients and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both *in vitro* and *in vivo*.

The term "a combined preparation", as used herein defines especially a "kit of parts" in the sense that the first and second active ingredient as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the ingredients, i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the active ingredients. The ratio of the total amounts of the active ingredient 1 to the active ingredient 2 to be administered in the combined preparation can be varied, e.g., in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the first and second active ingredient, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or both of the first and second active ingredient, and especially a strong synergism the first and second active ingredient.

It will be understood that in the discussion of methods, references to the active ingredients are meant to also include the pharmaceutically acceptable salts. If these active ingredients have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The active ingredients having an acid group (for example COOH) can also form salts with bases. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

A pharmaceutical combination which comprises two anti-epileptics selected from the list consisting of barbiturates and derivatives thereof, benzodiazepines, carboxamides, hydantoins, succinimides, valproic acid and other fatty acid derivates, AMPA antagonists and other anti-epileptic drugs, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, if at least one salt-forming group is present, will be referred to hereinafter as a COMBINATION OF THE INVENTION.

Surprisingly it was found that the administration of a COMBINATION OF THE INVENTION results in a beneficial, especially a synergistic, therapeutic effect or in other surprising beneficial effects, e.g. less side effects, compared to a monotherapy applying only one of the pharmaceutically active ingredients used in the COMBINATION OF THE INVENTION.

The pharmacological activity of a COMBINATION OF THE INVENTION may, for example, be evidenced in preclinical studies known as such, e.g. the Audiogenic Seizure Test or the methods described in the Examples.

The pharmacological activity of a COMBINATION OF THE INVENTION may, for example, be demonstrated in a clinical study. Such clinical studies are preferably randomized, double-blind, clinical studies in patients with epilepsy. Such studies demonstrate, in particular, the synergism of the active ingredients of the COMBINATIONS OF THE INVENTION. The beneficial effects on epilepsy can be determined directly through the results of these studies or by changes in the study design which are known as such to a person skilled in the art. The studies are, in particular, suitable to compare the effects of a monotherapy using the active ingredients and a COMBINATION OF THE INVENTION.

A further benefit is that lower doses of the active ingredients of the COMBINATION OF THE INVENTION can be used, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated. The COMBINATIONs OF THE INVENTION can be used, in particular, for the treatment of epilepsy which is refractory to monotherapy.

In one preferred embodiment of the invention, the COMBINATION OF THE INVENTION comprises a carboxamide.

In another preferred embodiment of the invention, the COMBINATION OF THE INVENTION comprises an AMPA antagonist.

Very preferred is a COMBINATION OF THE INVENTION comprising as active ingredients two anti-epileptic drugs, wherein a first anti-epileptic is selected from carboxamides, especially carbamazepine, oxcarbazepine, 10-hydroxy-10,11-dihydrocarbamazepine, a compound of formula II wherein R_1' represents acetoxy, tiagabine hydrochloride mono-hydrate, phenobarbital, levetiracetam and lamotrigine, and a second anti-epileptic is an AMPA antagonists.

Preferably, the AMPA antagonists used in the present invention are noncompetitive AMPA antagonists.

In one preferred embodiment of the invention, the AMPA antagonists used are quinoxalinedione aminoalkylphosphonates, in particular those of formula I, e.g. those disclosed in US 6,080,743, more preferably a compound of formula I wherein R_1 is hydroxy, R_2 is hydrogen, R_3 is nitro and X is methylene.

In another embodiment of the invention, the AMPA antagonists used is selected from CX691, EGIS8332 (7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-8-carbonitrile), GYKI47261 (4-(8-chloro-2-methyl-11H-imidazo[1,2-c][2,3]benzodiazepin-6-yl)benzenamine), Irampanel (BIIR561; N,N-dimethyl-2-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)phenoxy]ethanamine), KRP199 (7-[4-[[[[(4-carboxyphenyl)amino]-carbonyl]oxy]methyl]-1H-imidazol-1-yl]-3,4-dihydro-3-oxo-6-(trifluoromethyl)-2-quinoxaline-

carboxylic acid), NS1209 (2-[[[5-[4-[(dimethylamino)sulfonyl]phenyl]-1,2,6,7,8,9-hexahydro-8-methyl-2-oxo -3H-pyrrolo[3,2-h]isoquinolin-3-ylidene]amino]oxy]-4-hydroxybutanoic acid monosodium salt), topiramate (TOPAMAX, 2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate) and talampanel ((R)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine).

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against epilepsy, comprising at least two anti-epileptics or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. In this composition, the first and second active ingredient can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of at least one pharmacologically active ingredient, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application. The preferred route of administration of the dosage forms of the present invention is orally.

The novel pharmaceutical composition contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of active ingredient or ingredients contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils or alcohols; or carriers such as starches, sugars, microcristalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed.

Furthermore, the present invention relates to the use of a COMBINATION OF THE INVENTION for the preparation of a medicament for the treatment of epilepsy.

Additionally, the present invention provides a method of treating a warm-blooded animal having epilepsy comprising administering to the animal a COMBINATION OF THE INVENTION in a quantity which is jointly therapeutically effective against epilepsy and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.

Moreover, the present invention provides a commercial package comprising as active ingredients COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential use thereof in the treatment of epilepsy.

In particular, a therapeutically effective amount of each of the active ingredients of the COMBINATION OF THE INVENTION may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of treatment of diseases according to the invention may comprise (i) administration of the first active ingredient in free or pharmaceutically acceptable salt form and (ii) administration of the second active ingredient in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the amounts described herein. The individual active ingredients of the COMBINATION OF THE INVENTION can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a prodrug of an active ingredient that convert *in vivo* to the active ingredient. The instant invention is therefore to be

understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

In one preferred embodiment of the invention, the COMBINATION OF THE INVENTION is used for the treatment of treatment of epilepsy which is refractory to monotherapy.

The effective dosage of each of the active ingredients employed in the COMBINATION OF THE INVENTION may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the severity of the condition being treated. Thus, the dosage regimen the COMBINATION OF THE INVENTION is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of the active ingredients.

When the combination partners employed in the COMBINATION OF THE INVENTION are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the packet leaflet of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise. In particular,

Phenobarbital may be administered to an adult patient in a total daily dosage between about 1 to about 3 mg/kg body weight and to a paediatric patient in a total daily dosage between about 3 to about 4 mg/kg body weight, split into two separate units.

Primidone may be administered to an adult patient and to children being at least 9 years old in a total daily dosage of 0.75 to 1.5 g.

Clonazepam may be administered to an adult patient in a total daily dosage between about 3 to about 8 mg and to a paediatric patient in a total daily dosage between about 0.5 to about 3 mg, split into three of four separate units.

Diazepam may be administered to an adult patient in a total daily dosage between about 5 to about 10 mg and to a paediatric patient in a total daily dosage between about 5 to about 10 mg.

Lorazepam may be administered to an adult patient in a total daily dosage between about . 0.044 mg/kg body weight to about 0.05 mg/kg body weight.

Carbamazepine may be administered to an adult patient in a total daily dosage between about 600 to about 2000 mg and to a paediatric patient older than 6 years in a total daily dosage between about 400 to about 600 mg.

Oxcarbazepine may be administered to an adult patient in a total daily dosage between about 600 to about 2400 mg and to a paediatric patient in a total daily dosage between about 30 to about 46 mg/kg body weight.

Phenytoin may be administered to an adult patient in a total daily dosage between about 100 to about 300 mg and to a paediatric patient in a total daily dosage between about 100 to about 200 mg.

Ethosuximide may be administered to an adult patient in a total daily dosage of about 15 mg/kg body weight and to a paediatric patient in a total daily dosage of about 20 mg/kg body weight.

Valproic acid sodium salt may be administered to an adult patient in a total daily dosage of about 20 mg/kg body weight and to a paediatric patient in a total daily dosage of about 30 mg/kg body weight.

Tiagabine hydrochloride monohydrate may be administered to an adult patient in a total daily dosage between about 15 to about 70 mg.

Vigrabatrine may be administered to an adult patient in a total daily dosage between about 2 to about 3 g.

Levetiracetam may be administered to patient who is older than 16 years in a total daily dosage between about 1000 to about 3000 mg.

Lamotrigine may be administered to patient who is older than 12 years in a total daily dosage between about 100 to about 200 mg.

Gabapentin may be administered to patient in a total daily dosage between about 900 to about 2400 mg.

Sultiam may be administered to patient in a total daily dosage between about 5 to about 10 mg/kg body weight.

Felbamate may be administered to patient who is older than 14 years in a total daily dosage of between about 2400 to about 3600 mg.

Topiramate may be administered to an adult patient in a total daily dosage of between about 250 to about 500 mg.

The following Examples serve to illustrate the invention without limiting the invention in its scope.

Example 1: Maximal Electroshock Test-induced Seizures

Generalized tonic-clonic seizures are induced in mice by a maximal electroshock test (MES). In brief, seizures of the hind extremities of male Tif: MAGf (SPF) mice (19 - 25 g) are induced by passing alternating electrical current (50 Hz, 18 mA, 0.2 s) through temporal electrodes. The compounds and carbamazepine are suspended in 0.5% methyl cellulose for p.o. administration (doses for the compounds: 3.125, 6.25, 12.5 and 20.0 mg/kg p.o). The pre-treatment period for all compounds is 1 h. Ten animals per dose are used. For each experiment one group serves as a negative control (placebo). The number of animals

protected from tonic hind limb extension seizure is determined in each dose and combination group.

A compound of formula I wherein R_1 is hydroxy, R_2 is hydrogen, R_3 is nitro and X is methylene (compound **1**) combined with placebo consistently suppress MES-induced seizures in up to 50% of the mice at the doses of 3.125 to 20.0 mg/kg p.o. (pre-treatment period: 1 h). Carbamazepine at doses of 7.5 to 20.0 mg/kg p.o. combined with placebo protects up to 80% of the mice. The anticonvulsant effect of compound **1** doses combined with those of carbamazepine is more than additive in every possible case (Table 1).

Table 1

Compound **1** combined with:		% animals protected from seizures		
Compound	Dose	Placebo	Compound **1**, 3.125 mg/kg	Compound **1**, 6.25 mg/kg
Placebo	-	0%	0%	0%
Carbamazepine	7.5 mg/kg	0%	40%	
	12.5 mg/kg	20%	80%	
Carbamazepine	12.5 mg/kg	60%		90
	20.0 mg/kg	80%		100

Ten animals per dose.

What is claimed is:

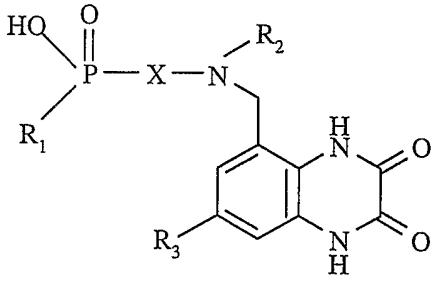
1. A combination comprising two anti-epileptics selected from the list consisting of barbiturates and derivatives thereof, benzodiazepines, carboxamides, hydantoins, succinimides, valproic acid and other fatty acid derivates, AMPA antagonists and other anti-epileptic drugs, in which the anti-epileptics are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

2. Combination according to claim 1 which is a combined preparation or a pharmaceutical composition.

3. Combination according to claim 1 or 2 comprising a carboxamide.

4. Combination according to any one of claims 1 to 3 comprising an AMPA antagonist.

5. Combination according to claim 1 or 2 wherein the two anti-epileptics are selected from carboxamides and an AMPA antagonist of formula I



I

wherein

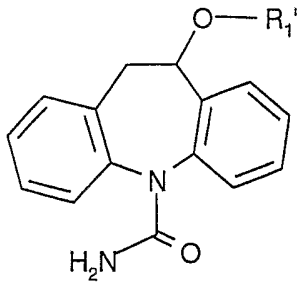
R_1 is hydroxy or (C_{1-4})alkyl,

R_2 is hydrogen or (C_{1-4})alkyl,

R_3 is hydrogen, (C_{1-4}) alkyl, fluorine, chlorine, bromine, trifluoromethyl, cyano or nitro, and

X is (C_{1-6})alkylene, (C_{1-6})alkylidene, (C_{1-6})alkylene(C_{3-6})cycloalkylene or (C_{1-6})alkylene-(C_{3-6})cycloalkylidene.

6. Combination according to claim 5 wherein the carboxamide is selected from carbamazepine, oxcarbazepine, 10-hydroxy-10,11-dihydrocarbamazepine and the compounds of formula II



(II)

wherein R_1' represents acetoxy.

7. Combination according to claim 5 or 6, wherein in the formula I R_1 is hydroxy, R_2 is hydrogen, R_3 is nitro and X is methylene.

8. Combination according to any one of claims 1 to 7 for simultaneous, separate or sequential use in the treatment of epilepsy.

9. Method of treating a warm-blooded animal having epilepsy comprising administering to the animal a combination according to any one of claims 1 to 7 in a quantity which is jointly therapeutically effective against epilepsy and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.

10. A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against epilepsy, of a pharmaceutical combination according to any one of claims 1 to 7 and at least one pharmaceutically acceptable carrier.

11. Use of a combination according to any one of claims 1 to 7 for the preparation of a medicament for the treatment of epilepsy.

12. Use according to claim 7 or 11 wherein the epilepsy is refractory to monotherapy.

13. A commercial package comprising a combination according to any one of claim 1 to 7 together with instructions for simultaneous, separate or sequential use thereof in the treatment of epilepsy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/498 A61K31/55 A61K45/06 A61P25/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 200066 Derwent Publications Ltd., London, GB; Class B05, AN 2000-673134 XP002291965 & CN 1 265 889 A (WANG X) 13 September 2000 (2000-09-13) abstract -----	1-3,8-13
X	ERNST MUTSCHLER: "Arzneimittelwirkungen - Lehrbuch der Pharmakologie und Toxikologie" 1997, WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT MBH STUTTGART , STUTTGART , XP002291963 page 252 - page 260 in particular p. 260 ----- -/--	1-3,8-13

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2004	06/09/2004

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

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARK H. BEERS, M.D., ROBERT BERKOW, M.D.: "The Merck Manual" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION, N.J. , XP002291964 page 1406 - page 1408	1-4,8-13
X	DAM M: "SUMMING UP OF THE SUCCESS SO FAR GAINED THROUGH CHOICE OF DRUGS OR COMBINATIONS OF DRUGS" ACTA NEUROLOGICA SCANDINAVICA SUPPLEMENTUM, vol. 69, no. 99, 1984, pages 19-22, XP009035076 & 3RD WORKSHOP ON MEMORY FUNCTIONS, GOTHENBURG, FEB. 4-6, 1983. ACTA NEUROL SCAND SUPPL. ISSN: 0065-1427 page 19	1-3,8-13
X	US 5 095 033 A (LEVY RENE H ET AL) 10 March 1992 (1992-03-10) column 1, line 39 - column 2, line 34 claims	1-3,8-13
X	WO 89/05642 A (FERKANY JOHN W ; PONTECORVO MICHAEL J (US)) 29 June 1989 (1989-06-29) page 6, last paragraph - page 7, paragraph 1 page 8 claims	1-3,8-13
X	GB 864 536 A (SAPOS S A LAB) 6 April 1961 (1961-04-06) page 2, left-hand column claims 2,3	1,2,8-13
X	US 3 489 836 A (WARING WILSON SHAW) 13 January 1970 (1970-01-13) abstract column 3, line 56 - line 59	1,2,8-13
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DECKERS C L P ET AL: "Selection of antiepileptic drug polytherapy based on mechanisms of action: The evidence reviewed" EPILEPSIA 2000 UNITED STATES, vol. 41, no. 11, 2000, pages 1364-1374, XP009035157 ISSN: 0013-9580	1-4,8-13
A	the whole document	5-7
X	ZARNOWSKI TOMASZ ET AL: "NBQX: A selective AMPA antagonist enhances antiepileptic properties of common anticonvulsant drugs against maximal electroshock in mice" POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY, vol. 44, no. SUPPL., 1992, pages 258-259, XP009035158 & XI CONGRESS OF THE POLISH PHARMACOLOGICAL SOCIETY AND OF THE GERMAN SOCIETY OF PHARMACOLOGY AND TOXI; GDANSK, POLAND; SEPTEMBER 16-19, 1992 ISSN: 0301-0244	1-4,8-13
A	the whole document	5-7
X	BOROWICZ KINGA K ET AL: "Interaction of GYKI 52466, a selective non-competitive antagonist of AMPA/kainate receptors, with conventional antiepileptic drugs in amygdala-kindled seizures in rats" POLISH JOURNAL OF PHARMACOLOGY, vol. 53, no. 2, March 2001 (2001-03), pages 101-108, XP009035159 ISSN: 1230-6002	1-4,8-13
A	the whole document	5-7
X	BOROWICZ KINGA K ET AL: "The non-competitive AMPA/kainate receptor antagonist, GYKI 52466, potentiates the anticonvulsant activity of conventional antiepileptics" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 281, no. 3, 1995, pages 319-326, XP002292362 ISSN: 0014-2999	1-4,8-13
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SWIADER MARIUSZ ET AL: "Influence of LY 300164, an AMPA/kainate receptor antagonist upon the anticonvulsant action of antiepileptic drugs against aminophylline-induced seizures in mice." POLISH JOURNAL OF PHARMACOLOGY, vol. 55, no. 1, January 2003 (2003-01), pages 103-107, XP009035160 ISSN: 1230-6002	1-4,8-13
A	the whole document	5-7
X	CZUCZWAR S J ET AL: "LY 300164, a novel antagonist of AMPA/kainate receptors, potentiates the anticonvulsive activity of antiepileptic drugs" EUROPEAN JOURNAL OF PHARMACOLOGY 1998 NETHERLANDS, vol. 359, no. 2-3, 1998, pages 103-109, XP002292363 ISSN: 0014-2999	1-4,8-13
A	abstract	5-7
X	WO 02/03915 A (KOZACHUK WALTER E) 17 January 2002 (2002-01-17) the whole document	1-4,8-13
A	WO 98/17692 A (HLYNIANSKI DANIEL RICHARD ; UNIV WALES BANGOR (GB)) 30 April 1998 (1998-04-30) cited in the application the whole document	
A	AUBERSON Y P ET AL: "N-phosphonoalkyl-5-aminomethylquinoxaline -2,3-diones: in vivo active AMPA and NMDA(glycine) antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 2, 18 January 1999 (1999-01-18), pages 249-254, XP004152611 ISSN: 0960-894X page 249	
P,X	WO 03/042182 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); SCHMUTZ MARKUS (CH)) 22 May 2003 (2003-05-22) the whole document	1-3,6-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/003518

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

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/003518

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