# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-505**

# ADMINISTRATIVE DOCUMENTS

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## PATENT CERTIFICATION STATEMENT

In the opinion and to the best knowledge of UCB Pharma, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs, other than the patents owned by UCB, Belgium.

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## SECTION 13. PATENT INFORMATION

UCB Pharma, Inc. believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if UCB Pharma, Inc. engages in the manufacture, use, and sale of Levetiracetam Tablets and/or Oral Solution.

The following patents claim the drug levetiracetam ((s)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide):

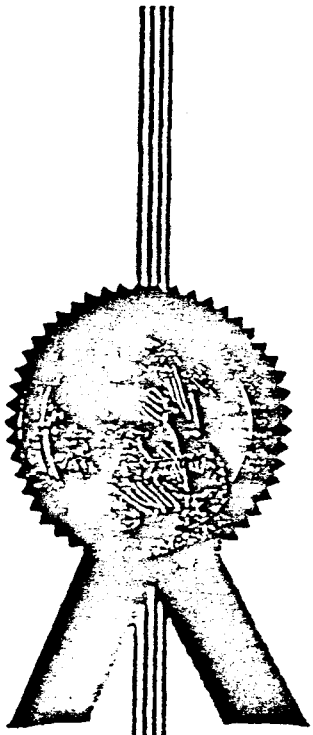
| | |
|---|---|
| Patent Number: | 4,943,639 |
| Date of Patent: | July 24, 1990 |
| Patent Expiration: | June 6, 2006 |
| Type of Patent: | Drug |
| Patent Owner: | UCB Societe Anonyme, Brussels, Belgium |
| U.S. Agent; | UCB Pharma, Inc. Smyrna, Georgia |

| | |
|---|---|
| Patent Number: | 4,837,223 |
| Date of Patent: | June 8, 1989 |
| Patent Expiration: | June 6, 2006 |
| Type of Patent: | Drug |
| Patent Owner: | UCB Societe Anonyme, Brussels, Belgium |
| U.S. Agent; | UCB Pharma, Inc. Smyrna, Georgia |

Both of these patents are owned by UCB, Belgium. Copies of the patents are attached.

Additionally, UCB requested a patent extension, which was published in the Federal Register on 25 January 2002. A copy is attached.

# The United States of America



## The Commissioner of Patents and Trademarks

*Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.*

*Therefore, this*

## United States Patent

*Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.*

Harry F. Manbeck, Jr.

Commissioner of Patents and Trademarks

Melvinia Gary

Attest

# United States Patent [19]

Gobert et al.

[11] Patent Number: 4,943,639

[45] Date of Patent: * Jul. 24, 1990


[54] (S)-ALPHA-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE


[75] Inventors: Jean Gobert, Brussels; Jean-Pierre Geerts, Leglise; Guy Bodson, Bellefontaine, all of Belgium

[73] Assignee: U C B Societe Anonyme, Brussels, Belgium



[*] Notice: The portion of the term of this patent subsequent to Jun. 6, 2006 has been disclaimed.

[21] Appl. No.: 311,631

[22] Filed: Feb. 16, 1989

Related U.S. Application Data

[62] Division of Ser. No. 25,271, Mar. 12, 1987, Pat. No. 4,837,223, which is a division of Ser. No. 733,790, May 24, 1985, Pat. No. 4,696,943.

[30] Foreign Application Priority Data

May 15, 1984 [GB] United Kingdom ..... 8412357

[51] Int. Cl.[5] ..... C07D 207/271

[52] U.S. Cl. ..... 548/550

[58] Field of Search ..... 548/546, 550; 514/424



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[57] ABSTRACT

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, its preparation and pharmaceutical compositions containing the same. It can be prepared either by reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with an alkyl haloformate and with ammonia, or, by cyclizing an (S)-2-amino-butanamide of the formula $X—CH_2CH_2—Y—NHCH(C_2H_5)CONH_2$ wherein Y is a $—CH_2—$ radical when X represents a ZOOC— radical and Y is a —CO— radical when X represents a $HalCH_2—$ radical, Z being a $C_1$-$C_4$ alkyl radical and Hal a halogen atom.

This laevorotatory enantiomer has been found to have significantly higher protective activity against hypoxia and ischemia than the corresponding racemate.


2 Claims, No Drawings

# (S)-ALPHA-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE

This application is a division of application Ser. No. 025,277, filed Mar. 12, 1987, now U.S. Pat. No. 4,837,223, which application is, in turn, a division of application Ser. No. 733,790, filed May 24, 1985, now U.S. Pat. No. 4,696,943.

The present invention relates to the novel compound (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, as well as to processes for the preparation thereof. It also relates to pharmaceutical compositions containing the said compound.

British Pat. No. 1,309,692 describes the compound alpha-ethyl-2-oxo-1-pyrrolidineacetamide (melting point 122° C.) and states that the compounds of this type can be used for therapeutic purposes, for example for the treatment of motion sickness, hyperkinesia, hypertonia and epilepsy.

Moreover, it also mentions that these compounds can be applied in field of memory disorders in normal or pathological conditions.

It is also known that alpha-ethyl-2-oxo-1-pyrrolidineacetamide possesses a protective activity against aggressions of the central nervous system caused by hypoxias, cerebral ischemia, etc. (Pharmarne,37/11,(1982), 753–765).

Continuing research work in this field, we have prepared and isolated the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide and have found that this compound differs in a completely unpredictable manner from the known racemic form, by

(1) having a 10 times higher protective activity against hypoxia (antihypoxia) and

(2) having a 4 times higher protective activity against ischemia (antiischemia).

As a result of this unexpected combination of properties the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide is more suitable for the treatment and prevention of hypoxic and ischemic type aggressions of the central nervous system. The important contribution of the hypoxic phenomenon in certain pathological conditions of the central nervous system suggests that this compound has a therapeutic effect in the treatment of the consequences of cerebral vascular accidents and of cranial traumas, of the sequelae of the ageing process or of circulatory insufficiencies of the central nervous system resulting from cerebral-ischemic or hypoxic accidents occurring for example during birth. The compound may also be used in hypoxic-type diseases of other organs or tissues, such as the heart and kidneys.

Accordingly, the present invention relates to the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide which has the S absolute configuration, the said compound being substantially free from the dextrorotatory enantiomer which has the R absolute configuration.

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention cannot be obtained directly from the racemic form by separating the two enantiomers. It can be prepared by one or other of the following processes:

(a) reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with (1) an alkyl haloformate of the formula HalCOOZ in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms



and with (2) ammonia. The alkyl haloformate is preferably ethyl chloroformate.

This reaction is generally carried out in dichloromethane at a temperature between −10° and −60° C.

The (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, used in this reaction, can be obtained from the racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by chemical resolution in accordance with methods known per se, for example by forming a salt of this acid with an optically active base and isolating the salt formed with (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by successive crystallizations an appropriate solvent (for example benzene).

By way of examples of optically active bases which can be used for this resolution there may be mentioned alkaloids such as brucine, quinine strychnine, quinidine and cinchonidine and amines such as alpha-methylbenzylamine and dehydroabietylamine (cf. S. H. WILEN et al., Tetrahedron, 33,(1977),2725–2736). Particularly favourable results are obtained by using alpha-methylbenzylamine and dehydroabietylamine.

The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used as the starting material can be obtained by saponifying the corresponding alkyl ester, the synthesis of which has been described in British Pat. No. 1,309,692.

(b) cyclizing an (S)-2-amino-butanamide of the formula

$$X—CH_2CH_2—Y—NHCH(C_2H_5)CONH_2 \quad (A)$$

in which

X represents a ZOOC— or $HalCH_2$— radical, Z being an alkyl radical having 1 to 4 carbon atoms, and Hal a halogen atom, preferably chlorine or bromine, and

Y represents a $—CH_2—$ or —CO— radical,

with the proviso that Y is a $—CH_2—$ radical when X represents a ZOOC— radical and Y is a —CO— radical when X represents a $HalCH_2$— radical. The cyclization of the (S)-2-amino-butanamide of formula A is carried out in an inert solvent, such as toluene or dichloromethane, at a temperature of from 0° C. to the boiling point of the solvent. This cyclization is advantageously carried out in the presence of a basic substance as a catalyst. This catalyst is preferably 2-hydroxypyridine when the compound of formula A is an ester (X = ZOOC—) and tetrabutylammonium bromide when the compound of formula A is a halide (X = $HalCH_2$—).

When X represents a ZOOC— radical and Y is a $—CH_2—$ radical the compound of formula A is an alkyl (S)-4-[[1-(aminocarbonyl)propyl]amino]butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$, in which Z has the meaning given above. The latter can be prepared by condensing (S)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2Hal$, in which Z has the meaning given above and Hal is a halogen atom.

When X represents a $HalCH_2$— radical and Y is thus a —CO— radical, the compound of formula A is (S)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2CONHCH(C_2H_5)CONH_2$, in which Hal has the meaning given above. This latter compound can be prepared by condensing (S)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, in which Hal is a halogen atom.

The reaction between the (S)-2-amino-butanamide on the one hand and the alkyl 4-haloburyrate or 4-halobutyryl halide on the other hand, is generally carried out: in an inert solvent, such as benzene, toluene, dichloromethane or acetonitrile, at a temperature of from −5° to −100° C. and in the presence of an acid acceptor such as a ternary organic base ((for example triethylamine) or an inorganic base (for example potassium carbonate or hydroxide or sodium carbonate or hydroxide).

When X represents a $Hal-CH_2-$ radical and Y a —CO— radical, it is not absolutely necessary to isolate the compound of formula A obtained from the starting materials mentioned above. In fact, the compound of formula A, obtained in situ, can be cyclized directly to the (S)-alphaethyl-2-oxo-1-pyrrolidineacetamide according to the present invention (see Example 4 below).

The (S)-2-amino-butanamide used as starting material can be obtained from (S)-2-amino-butyric acid by ammonolysis of the corresponding methyl ester in accordance with the method described by K. FOLKERS et al in J.Med.Chem. 14,(6),(1971),484–487.

The following examples are given for the purpose of illustration only.

In these examples, the optical purity of the compounds obtained was verified by calorimetric determination of the differential enthalpies (C. FOUQUEY and J. JACQUES, Tetrahedron 23,(1967),4009–19).

## EXAMPLE 1

### (a) Preparation of the (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid

8.7 kg (50.8 moles) of racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 21.5 liters of anhydrous benzene in a 50 liter reactor. To this suspension is added gradually a solution containing 3.08 kg (25.45 moles) of (R)-(+)-alpha-methyl-benzylamine and 2.575 kg (25.49 moles) of triethylamine in 2.4 liters of anhydrous benzene. This mixture is then heated to reflux temperature until complete dissolution. It is then cooled and allowed to crystallize for a few hours. 5.73 kg of the (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained.

Melting point: 148°–151° C. Yield: 77.1%.

This salt may be purified by heating under reflux in 46.3 liters of benzene for 4 hours. The mixture is cooled and filtered to obtain 5.040 kg of the desired salt. Melting point: 152°–153.5° C. Yield: 67.85%.

### (b) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid

5.04 kg of the salt obtained in (a) above are dissolved in 9 liters of water. 710 g of a 30% sodium hydroxide solution are added slowly so that the pH of the solution reaches 12.6 and the temperature does not exceed 25° C. The solution is stirred for a further 20 minutes and the alpha-methylbenzylamine liberated is extracted repeatedly with a total volume of 18 liters of benzene.

The aqueous phase is then acidified to a pH of 1.1 by adding 3.2 liters of 6N hydrochloric acid. The precipitate formed is filtered off, washed with water and dried.

The filtrate is extracted repeatedly with a total volume of 50 liters of dichloromethane. The organic phase is dried over sodium sulfate and filtered and evaporated to dryness under reduced pressure.

The residue obtained after the evaporation and the precipitate isolate previously, are dissolved together in 14 liters of hot dichloromethane. The dichloromethane is distilled and replaced at the distillation rate, by 14 liters of toluene from which the product crystallizes.

The mixture is cooled to ambient temperature and the crystals are filtered off to obtain 2.78 kg of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid.

Melting point: 125.9° C. $[alpha]_D^{20} = -26.4°$ (c = 1, acetone). Yield: 94.5%.

### (c) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

34.2 g (0.2 mole) of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 225 ml of dichloromethane cooled to −30° C. 24.3 g (0.24 mole) of triethylamine are added dropwise over 15 minutes. The reaction mixture is then cooled to −40° C. and 24.5 g (0.224 mole) of ethyl chloroformate are added over 12 minutes. Thereafter, a stream of ammonia is passed through the mixture for 4½ hours. The reaction mixture is then allowed to return to ambient temperature and the ammonium salts formed are removed by filtration and washed with dichloromethane. The solvent is distilled off under reduced pressure. The solid residue thus obtained is dispersed in 55 ml toluene and the dispersion is stirred for 30 minutes and then filtered. The product is recrystallized from 280 ml of ethyl acetate in the presence of 9 g of 0.4 nm molecular sieve in powder form.

24.6 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are obtained.

Melting point: 115°–118° C. $[alpha]_D^{25} = -89.7°$ (c = 1, acetone). Yield: 72.3%.

Analysis for $C_8H_{14}N_2O_2$ in %: calculated: C 56.45, H 8.29, N 16.46; found: 56.71, 8.22, 16.48.

The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used in this synthesis has been prepared in the manner described below.

A solution containing 788 g (19.7 moles) of sodium hydroxide in 4.35 liters of water is introduced over 2 hours into a 20 liter flask containing 3.65 kg (18.34 moles) of ethyl (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetate at a temperature not exceeding 60° C. When this addition is complete, the temperature of the mixture is raised to 80° C. and the alcohol formed is distilled off until the temperature of the reaction mixture reaches 100° C.

The reaction mixture is then cooled to 0° C. and 1.66 liter (19.8 moles) of 12N hydrochloric acid is added over two and a half hours. The precipitate formed is filtered off, washed with 2 liters of toluene and recrystallized from isopropyl alcohol. 2.447 kg of racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, melting at 155°–156° C., are thus obtained. Yield: 78%.

Analysis for $C_8H_{13}NO_3$ in %: calculated: C 56.12, H 7.65, N 8.18; found: 55.82, 8.10, 7.97.

## EXAMPLE 2

### (a) Preparation of ethyl (S)-4-[[1-(aminocarbonyl)propyl]amino]butyrate

143.6 ml (1.025 mole) of triethylamine are added to a suspension of 47.75 g (0.345 mole) of (S)-2-amino-butanamide hydrochloride ($[alpha]_D^{25}$: +26.1°; c = 1, methanol) in 400 ml of toluene. The mixture is heated to 80° and 67.2 g (0.345 mole) of ethyl 4-bromoburyrate are introduced dropwise.

The reaction mixture is maintained at 80° C. for 10 hours and then filtered hot to remove the triethylamine salts. The filtrate is then evaporated under reduced pressure and 59 g of an oily residue consisting essen-

nally of the monoalkylation product but containing also a small amount of dialkylated derivative are obtained.

The product obtained in the crude state has been used as such, without additional purification, in the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide by cyclization.

(b) Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

54 g of the crude product obtained in a) above are dissolved in 125 ml of toluene in the presence of 2 g of 2-hydroxypyridine. The mixture is heated at 110° C. for 12 hours.

The insoluble matter is filtered off hot and the filtrate is then evaporated under reduced pressure.

The residue is purified by chromatography on a column of 1.1 kg of silica (column diameter: 5 cm; eluent: a mixture of ethyl acetate, methanol and concentrated ammonia solution in a proportion by volume of 85:12:3).

The product isolated is recrystallized from 50 ml of ethyl acetate to obtain 17.5 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

Melting point: 117° C. $[alpha]_D^{25}$: −90.0° (c=1, acetone). Yield: 41%.

## EXAMPLE 3

(a) Preparation of
(S)-N-[1(aminocarbonyl)propyl]-4-chlorobutanamide

345.6 g (2.5 moles) of ground potassium carbonate are mixed with 138.5 g (1 mole) of (S)-2-amino-butanamide hydrochloride in 2.5 liters of acetonitrile. The reaction mixture is cooled to 0° C. and a solution of 129.2 g (1.2 mole) of 4-chlorobutyryl chloride in 500 ml of acetonitrile is introduced dropwise. After the addition, the reaction mixture is allowed to return to ambient temperature; the insoluble matter is filtered off and the filtrate evaporated under reduced pressure. The crude residue obtained is stirred in 1.2 liter of anhydrous ether for 30 minutes at a temperature between 5° and 10° C. The precipitate is filtered off, washed twice with 225 ml of ether and dried in vacuo to obtain 162.7 g of (S)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide.

Melting point: 118°–123° C. $[alpha]_D^{25}$: −18° (c=1, methanol). Yield: 78.7%.

The crude product thus obtained is very suitable for the cyclization stage which follows. It can however be purified by stirring for one hour in anhydrous ethyl acetate.

Melting point: 120°–122° C. $[alpha]_D^{25}$: −22.2° (c=1, methanol).

(b) Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

6.2 g (0.03 mole) of (S)-N-[1(aminocarbonyl)propyl]-4-chlorobutanamide and 0.484 g (0.0015 mole) of tetrabutylammonium bromide are mixed in 45 ml of dichloromethane at 0° C. under a nitrogen atmosphere. 2.02 g (0.036 mole) of potassium hydroxide powder are added over 30 minutes, at such a rate that the temperature of the reaction mixture does not exceed +2° C. The mixture is then stirred for one hour, after which a further 0.1 g (0.0018 mole) of ground potassium hydroxide is added and stirring continued for 30 minutes at 0° C. The mixture is allowed to return to ambient temperature. The insoluble matter is filtered off and the filtrate is concentrated under reduced pressure. The residue obtained is recrystallized from 40 ml of ethyl acetate in the presence of 1.9 g of 0.4 nm molecular sieve. The latter is removed by hot filtration to give 3.10 g of (S)-alphaethyl-2-oxo-1-pyrrolidineacetamide.

Melting point: 116.7° C. $[alpha]_D^{25}$: −90.1° (c=1, acetone). Yield: 60.7%.

## EXAMPLE 4

Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

This example illustrates a variant of the process of Example 3, in which the intermediate 4-chlorobutanamide obtained in situ is not isolated. 84 g of anhydrous sodium sulfate are added to a suspension of 69.25 g (0.5 mole) of (S)-2-amino-butanamide hydrochloride in 600 ml of dichloromethane at ambient temperature. The mixture is cooled to 0° C. and 115 g of ground potassium hydroxide are added, followed by 8.1 g (0.025 mole) of tetrabutylammonium bromide dissolved in 100 ml of dichloromethane. A solution of 77.5 g of 4-chlorobutyryl chloride in 100 ml of dichlorometha is added dropwise at 0° C., with vigorous stirring. After 5 hours' reaction, a further 29 g of ground potassium hydroxide are added. Two hours later, the reaction mixture is filtered over Hyflo-cel and the filtrate evaporated under reduced pressure. The residue (93.5 g) is dispersed in 130 ml of hot toluene for 45 minutes. The resultant mixture is filtered and the filtrate evaporated under reduced pressure. The residue (71.3 g) is dissolved hot in 380 ml of ethyl acetate to which 23 g of 0.4 nm molecular sieve in powder form are added. This mixture is heated to reflux temperature and filtered hot. After cooling the filtrate, the desired product crystallizes to give 63 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

Melting point: 117° C. $[alpha]_D^{25}$: −91.3° (c=1, acetone). Yield: 74.1%.

### Pharmacological tests

Racemic alpha-ethyl-2-oxo-1-pyrrolidineacetamide (compound A) and (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide (compound B) of the present invention were subjected to pharmacological tests.

1. Protection against hypoxia (mouse)

a. Principle (C. GIURGEA and F. MOURAVIEFF-LESUISSE; Proc.Xth Intern. Congr. of the Coll. Intern. Neuro-psych - Pergamon Press, Oxford and New York, 1978, p.1623–1631).

The principle of this test lies in measuring the possibilities of survival of the organism subjected to an atmosphere in which the oxygen level is progressively decreased. Due to the particular sensitivity of the nervous system to this type of aggression, the results obtained in this test can be interpreted as a measure of the resistance of the central nervous system. Compounds which increase the resistance of the animals to this stress are suitable for the treatment and prevention of hypoxic type aggressions of the central nervous system.

b. Method

The apparatus consists of an airtight transparent cage 37 cm high, 39 cm deep and 97 cm wide. This 140 liter cage is provided with 60 transparent compartments each 6×10×10 cm, making it possible to separately accomodate 60 mice.

A fan ensures circulation of the atmosphere between the compartments through a grid floor. The cage is equipped with a device for introducing nitrogen at a constant flow rate, and with an orifice communicating

with the ambient atmosphere. Male mice (NMRI strain) weighing 20 to 22 g, are kept fasting as from the day before the test. The experiment is effected on the following day, simultaneously on 3 groups of 20 mice: a control group is given water (25 ml/kg) orally, and the other two groups are each given orally a compound to be tested.

25 minutes after the administration, the animals are distributed at random amongst the compartments so that none of the three groups is concentrated in a preferred area of the cage.

30 minutes after administration, the cage is closed and nitrogen is admitted into it at a constant flow rate (7.75 liters of technical grade nitrogen per minute) for about 37 minutes, at which stage the atmosphere contains 3.7% oxygen.

The cage is left closed until the critical moment where no more than 3 survivors are observed among the 20 control animals. At that moment, the cage is opened and atmospheric air admitted into it. A few moments later the survivors in each group of animals are counted.

For each dose of compound to be tested, the experiments are repeated once or twice, and the results pooled to obtain a minimum of 40 (or 60 animals treated per dose and 40 (or 60) corresponding control animals. For each dose of compound tested, the number of surviving animals among those treated with the compound is compared with the number of surviving animals among the control animals. The difference between these numbers expresses the protective activity of the compound against hypoxia caused by oxygen deprivation. The statistical significance (P) of this difference is evaluated by the Fischer-Yates test.

c. Results

Table I below gives the results obtained for increasing doses of compounds A and B.

TABLE I

| Compound tested | Oral dose in mmol/kg | Number of surviving animals: control | Number of surviving animals: treated | P |
|---|---|---|---|---|
| A | 0.012 | 12/40 | 16/80 | NS |
| | 0.1 | 8/80 | 7/80 | NS |
| | 0.16 | 12/80 | 12/80 | NS |
| | 0.32 | 10/80 | 30/80 | <0.001 |
| B | 0.016 | 5/40 | 11/40 | NS |
| | 0.032 | 8/40 | 17/40 | <0.6 |
| | 0.1 | 6/40 | 19/40 | <0.005 |
| | 0.16 | 6/40 | 19/40 | <0.005 |
| | 0.32 | 5/40 | 17/40 | <0.01 |

NS = [illegible]

d. Conclusions

In this test, the laevorotatory enantiomer of the invention (compound B) increases the survival of the animals deprived of oxygen when administered at doses from 0.032 mmol/kg upwards. The racemate (compound A) exerts a similar activity only from 0.32 mmol/kg upwards (1st effective dose). Thus, the laevorotatory enantiomer of the present invention is 10 times more active than the corresponding racemate.

II. Protection against cerebral ischemia (rats)

a. Principle (C. GIURGEA and F. MOURAVIEFF-LESUISSE; see above under Ia.) Electroencephalographic controls have shown that the ligature of the 2 common carotids in the rat causes a true cerebral ischemia: the electroencephalogram trace flattens and ever becomes isoelectric (electric silence).

b. Method

Male Wistar rats weighing between 250 and 350 g are anesthetized with pentobarbital administered intraperitoneally at a dose of 50 mg/kg (0.5 ml/100 g).

Immediately after the anesthesia, the animals are administered intraperitoneally with an amount of 0.5 ml/100 g, either the compound to be tested dissolved in an isotonic sodium chloride solution (treated animals), or only an isotonic sodium chloride solution or placebo (control animals). About 20 minutes later, the 2 common carotids are exposed and about 10 minutes later ligatured simultaneously. This operation is effected simultaneously on the control animals and the treated animals.

An hour after administration of the compound to be tested or of the placebo, there is again administered intraperitoneally the same dose of either the compound to be tested (to the treated animals) or the place (to the control animals).

5 hours after the first administration, there is administered for the third time the same dose of either the compound to be tested (to the surviving treated animals) or the placebo (to the surviving control animals).

24 hours after the first administration the efficacy of the ligature is verified in all animals, under pentobarbital anesthesia, by section of the carotids downstream of the ligature. The number of surviving animals is recorded among both the treated animals and the control animals. For each dose of compound tested, the number of surviving animals among those treated with the compound is compared with the number of surviving animals among the control animals. The difference expresses the protective activity of the compound against the lethality induced by the simultaneous ligature of the 2 carotids. The statistical significance (P) of this difference is evaluated by the Brandt-Snedecor test.

c. Results

Table II below gives the results obtained for increasing doses of compounds A and B.

TABLE II

| Compound tested | Intraperitoneal dose in mmol/kg | Number of surviving animals: control | Number of surviving animals: treated | P |
|---|---|---|---|---|
| A | 0.32 | 6/29 | 8/29 | NS |
| | 0.64 | 11/30 | 21/30 | 0.01 |
| B | 0.1 | 9/29 | 14/29 | NS |
| | 0.16 | 6/29 | 14/30 | 0.05 |
| | 0.32 | 8/30 | 19/29 | 0.01 |

NS = [illegible]

d. Conclusions

Table II shows that the racemate (compound A) is only active from a dose of 0.64 mmol/kg upwards. In contrast, the laevorotatory enantiomer of the invention (compound B) protects the animals, from 0.16 mmol/kg upwards, against the lethality induced by the simultaneous ligature of the two carotids and thus proves to be 4 times more active than the racemate.

III. Toxicity

Table III below gives, for compounds A and B, the $LD_{50}$, in mg/kg, determined on the male mouse and the male rat after intravenous administration:

TABLE III

| Compound tested | $LD_{50}$ in mg/kg | |
|---|---|---|
| | mouse | rat |
| A | 1790 | 1500 |
| B | 1081 | 1038 |

As can be seen from this table the laevorotatory enantiomer of the invention (compound B) has, like the racemate (compound A), very low toxicity and the toxic dose is well above the active dose.

The compound of the present invention can be administered either orally in the form of solid or liquid compositions for example, in the form of tablets, pills, degrees, gelatine capsules, solutions or syrups, or parenterally in the form of injectable solutions or suspensions. Pharmaceutical forms such as solutions or tablets are prepared according to conventional pharmaceutical methods. The compound of the invention may be mixed with a solid or liquid non-toxic pharmaceutically acceptable carrier and optionally with a dispersant, a stabilizer and where necessary, colorants and sweeteners.

Similarly the solid or liquid pharmaceutical carriers used in these compositions are well known.

Solid pharmaceutical excipients for the preparation of tablets or capsules include, for example, starch, talc, calcium carbonate, lactose, sucrose and magnesium stearate.

The percentage of active product in the pharmaceutical compositions can vary within very wide limits depending upon the mode of administration and the condition of the patient. The human posology can vary between 250 mg and 3 g per day.

There is given below a non-limiting example of a composition containing the compound of the invention i.e. a 100 mg gelanne capsule for oral administration:

| | |
|---|---|
| compound B | 100 mg |
| avicel (microcrystalline cellulose) | 217 mg |
| Mg stearate | 3 mg |

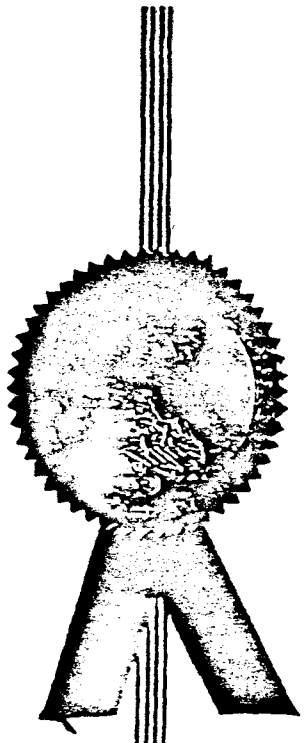
We claim:

1. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

2. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, prepared by the process which comprises reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with (1) an alkyl haloformate of the formula HalCOOZ in which Hal represents a halogen atom and Z represents an alkyl radical having 1 to 4 carbon atoms, and with (2) ammonia.

* * * * *

# The United States of America



## The Commissioner of Patents and Trademarks

*Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.*

*Therefore, this*

## United States Patent

*Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.*

*Commissioner of Patents and Trademarks*

*Attest*

United States Patent [19]
Gobert et al.

[11] Patent Number: 4,837,223
[45] Date of Patent: * Jun. 6, 1989

[54] (S)-ALPHA-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE COMPOSITIONS

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[*] Notice: The portion of the term of this patent subsequent to Jun. 6, 2006 has been disclaimed.

[21] Appl. No.: 25,277

[22] Filed: Mar. 12, 1987

Related U.S. Application Data

[62] Division of Ser. No. 733,790, May 14, 1985, Pat. No. 4,696,943.

[30] Foreign Application Priority Data

May 15, 1984 [GB] United Kingdom ..... 84/12357

[51] Int. Cl.[4] ..... C07D 207/273; A61K 31/40
[52] U.S. Cl. ..... 514/424; 548/543
[58] Field of Search ..... 548/543; 514/424

[56] References Cited

FOREIGN PATENT DOCUMENTS

2081506 12/1971 France .
2368275 5/1978 France .

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*Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack

[57] ABSTRACT

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, its preparation and pharmaceutical compositions containing the same. It can be prepared either by reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with an alkyl haloformate and with ammonia, or, by cyclizing an (S)-2-amino-butanamide of the formula $X—CH_2CH_2-NHCH(C_2H_5)CONH_2$ wherein Y is a $—CH_2—$radical when X represents a ZOOC—radical and Y is a —CO— radical when X represents a $HalCH_2—$radical, Z being a $C_1–C_4$ alkyl radical and Hal a halogen atom.

This laevorotatory enantiomer has been found to have significantly higher protective activity against hypoxia and ischemia than the corresponding racemate.

2 Claims, No Drawings

# (S)-ALPHA-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE COMPOSITIONS

This application is a division of application Ser. No. 733,790 filed May 14, 1985, now U.S. Pat. No. 4,696,943.

The present invention relates to the novel compound (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, as well as to processes for the preparation thereof. It also relates to pharmaceutical compositions containing the said compound.

British Pat. No. 1,309,692 describes the compound alpha-ethyl-2-oxo-1-pyrrolidineacetamide (melting point 122° C.) and states that the compounds of this type can be used for therapeutic purposes, for example for the treatment of motion sickness, hyperkinesia, hypertonia and epilepsy.

Moreover, it also mentions that these compounds can be applied in the field of memory disorders in normal or pathological conditions.

It is also known that alpha-ethyl-2-oxo-1-pyrrolidineacetamide possesses a protective activity against aggressions of the central nervous system caused by hypoxias, cerebral ischemia, etc. (Pharmazie, 37/11, (1982), 753–765).

Continuing research work in this field, we have prepared and isolated the levorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide and have found that this compound differs in a completely unpredictable manner from the known racemic form, by

(1) having a 10 times higher protective activity against hypoxia (antihypoxia) and

(2) having a 4 times higher protective activity against ischemia (antiischemia).

As a result of this unexpected combination of properties the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide is more suitable for the treatment and prevention of hypoxic and ischemic type aggressions of the central nervous system. The important contribution of the hypoxic phenomenon in certain pathological conditions of the central nervous system suggests that this compound has a therapeutic effect in the treatment of the consequences of cerebral vascular accidents and of cranial traumas, of the sequels of the ageing process or of circulatory insufficiencies of the central nervous system resulting from cerebral-ischemic or hypoxic accidents occurring for example during birth. The compound may also be used in hypoxic-type diseases of other organs or tissues, such as the heart and kidneys.

Accordingly, the present invention relates to the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide which has the S absolute configuration, the said compound being substantially free from the dextrorotatory enantiomer which has the R absolute configuration.

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention cannot be obtained directly from the racemic form by separating the two enantiomers. It can be prepared by one or other of the following processes:

(a) reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with (1) an alkyl haloformate of the formula HalCOOZ in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms and with (2) ammonia. The alkyl haloformate is preferably ethyl chloroformate.



This reaction is generally carried out in dichloromethane at a temperature between −10° and −60° C.

The (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, used in this reaction, can be obtained from the racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by chemical resolution in accordance with methods known per se, for example by forming a salt of this acid with an optically active base and isolating the salt formed with (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by successive crystallizations in an appropriate solvent (for example benzene).

By way of examples of optically active bases which can be used for this resolution there may be mentioned alkaloids such as brucine, quinine, strychnine, quinidine and cinchonidine and amines such as alpha-methyl-benzylamine and dehydroabietylamine (cf. S. H. WILEN et al., Tetrahedron, 33, (1977), 2725–2736). Particularly favourable results are obtained by using alpha-methyl-benzylamine and dehydroabietylamine. The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used as the starting material can be obtained by saponifying the corresponding alkyl esters, the synthesis of which has been described in British Pat. No. 1,309,692.

(b) cyclizing an (S)-2-amino-butanamide of the formula

$$X—CH_2CH_2—Y—NHCH(C_2H_5)CONH_2 \quad (A)$$

in which

X represents a ZOOC— or $HalCH_2$— radical, Z being an alkyl radical having 1 to 4 carbon atoms, and Hal a halogen atom, preferably chlorine or bromine, and

Y represents a $—CH_2—$ or —CO— radical,

with the proviso that Y is a $—CH_2—$ radical when X represents a ZOOC— radical and Y is a —CO— radical when X represents a $HalCH_2$— radical. The cyclization of the (S)-2-amino-butanamide of formula A is carried out in an inert solvent, such as toluene or dichloromethane, at a temperature of from 0° C. to the boiling point of the solvent. This cyclization is advantageously carried out in the presence of a basic substance as a catalyst. This catalyst is preferably 2-hydroxypyridine when the compound of formula A is an ester (X=ZOOC—) and tetrabutylammonium bromide when the compound of formula A is a halide ($X=HalCH_2$—).

When X represents a ZOOC— radical and Y is a $—CH_2—$ radical the compound of formula A is an alkyl (S)-4-[(1-aminocarbonyl)propyl]amino]butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$, in which Z has the meaning given above. The latter can be prepared by condensing (S)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2Hal$, in which Z has the meaning given above and Hal is a halogen atom.

When X represents a $HalCH_2$— radical and Y is thus a —CO— radical, the compound of formula A is (S)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2CONHCH(C_2H_5)CONH_2$, in which Hal has the meaning given above. This latter compound can be prepared by condensing (S)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, in which Hal is a halogen atom.

The reaction between the (S)-2-amino-butanamide on the one hand and the alkyl 4-halobutyrate or 4-halobutyryl halide on the other hand, is generally carried out

an aromatic solvent, such as benzene, toluene, dichloromethane or acetonitrile, at a temperature of from −5° to −10° C. and in the presence of an acid acceptor such as a tertiary organic base (for example triethylamine) or an inorganic base (for example potassium carbonate or hydroxide or sodium carbonate or hydroxide).

When X represents a $HalCH_2$— radical and Y a —CO— radical, it is not absolutely necessary to isolate the compound of formula A obtained from the starting materials mentioned above. In fact, the compound of formula A, obtained in situ, can be cyclized directly to the (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention (see Example 4 below).

The (S)-2-amino-butanamide used as starting material can be obtained from (S)-2-amino-butyric acid by ammonolysis of the corresponding methyl ester in accordance with the method described by K. FOLKERS et al in J. Med. Chem. 14, (6), (1971), 484–487.

The following examples are given for the purpose of illustration only.

In these examples, the optical purity of the compounds obtained was verified by calorimetric determination of the differential enthalpies (C. FOUQUEY and J. JACQUES, Tetrahedron, 23, (1967), 4005–19).

## EXAMPLE 1

### (a) Preparation of the (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid

8.7 kg (50.8 moles) of racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 21.5 liters of anhydrous benzene in a 50 liter reactor. To this suspension is added gradually a solution containing 3.08 kg (25.45 moles) of (R)-(+)-alpha-methyl-benzylamine and 2.575 kg (25.45 moles) of triethylamine in 2.4 liters of anhydrous benzene. This mixture is then heated to reflux temperature until complete dissolution. It is then cooled and allowed to crystallize for a few hours. 5.73 kg of the (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained.

Melting point: 148°–151° C. Yield: 77.1%.

This salt may be purified by heating under reflux in 42.3 liters of benzene for 4 hours. The mixture is cooled and filtered to obtain 5.040 kg of the desired salt.

Melting point: 152°–153.5° C.

Yield: 67.85%.

### (b) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid

5.04 kg of the salt obtained in (a) above are dissolved in 9 liters of water. 710 g of a 30% sodium hydroxide solution are added slowly so that the pH of the solution reaches 12.6 and the temperature does not exceed 25° C. The solution is stirred for a further 20 minutes and the alpha-methyl-benzylamine liberated is extracted repeatedly with a total volume of 18 liters of benzene.

The aqueous phase is then acidified to a pH of 1.1 by adding 3.2 liters of 6N hydrochloric acid. The precipitate formed is filtered off, washed with water and dried.

The filtrate is extracted repeatedly with a total volume of 50 liters of dichloromethane. The organic phase is dried over sodium sulfate and filtered and evaporated to dryness under reduced pressure.

The residue obtained after the evaporation and the precipitate isolate previously, are dissolved together in 14 liters of hot dichloromethane. The dichloromethane is distilled and replaced at the distillation rate, by 14 liters of toluene from which the product crystallizes.

The mixture is cooled to ambient temperature and the crystals are filtered off to obtain 2.78 kg of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid.

Melting point: 125.5° C.

$[alpha]_D^{20} = -26.4°$ (c = 1, acetone)

Yield: 94.5%.

### (c) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

34.2 g (0.2 mole) of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 225 ml of dichloromethane cooled to −30° C. 24.3 g (0.24 mole) of triethylamine are added dropwise over 15 minutes. The reaction mixture is then cooled to −40° C. and 24.3 g (0.224 mole) of ethyl chloroformate are added over 12 minutes. Thereafter, a stream of ammonia is passed through the mixture for 4½ hours. The reaction mixture is then allowed to return to ambient temperature and the ammonium salts formed are removed by filtration and washed with dichloromethane. The solvent is distilled off under reduced pressure. The solid residue thus obtained is dispersed in 55 ml toluene and the dispersion is stirred for 30 minutes and then filtered. The product is recrystallized from 280 ml of ethyl acetate in the presence of 9 g of 0.4 nm molecular sieve in powder form.

24.6 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are obtained.

Melting point: 115°–118° C.

$[alpha]_D^{23} = -89.7°$ (c = 1, acetone).

Yield: 72.3%.

Analysis for $C_8H_{14}N_2O_2$ in %: calculated: C 56.45; H 8.29; N 16.46; found: 56.71; 8.22; 16.48;

The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used in this synthesis has been prepared in the manner described below.

A solution containing 788 g (19.7 moles) of sodium hydroxide in 4.35 liters of water is introduced over 2 hours into a 20 liter flask containing 3.65 kg (18.34 moles) of ethyl (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetate at a temperature not exceeding 60° C. When this addition is complete, the temperature of the mixture is raised to 80° C. and the alcohol formed is distilled off until the temperature of the reaction mixture reaches 100° C.

The reaction mixture is then cooled to 0° C. and 1.66 liter (19.8 moles) of 12N hydrochloric acid is added over two and a half hours. The precipitate formed is filtered off, washed with 2 liters of toluene and recrystallized from isopropyl alcohol. 2.447 kg of racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, melting at 155°–156° C., are thus obtained.

Yield: 78%.

Analysis for $C_8H_{13}NO_3$ in %: calculated: C 56.12; H 7.65; N 8.18, found: 55.82; 8.10; 7.97;

## EXAMPLE 2

### (a) Preparation of ethyl (S)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate

143.6 ml (1.035 mole) of triethylamine are added to a suspension of 47.75 g (0.345 mole) of (S)-2-amino-butanamide hydrochloride ($[alpha]_D^{25}$: −26.1°; c = 1, methanol) in 400 ml of toluene. The mixture is heated to 80° C. and 67.2 g (0.345 mole) of ethyl 4-bromobutyrate are introduced dropwise.

The reaction mixture is maintained at 80° C. for 10 hours and then filtered hot to remove the triethylamine salts. The filtrate is then evaporated under reduced pressure and 59 g of an oily residue consisting essentially of the monoalkylation product but containing also a small amount of dialkylated derivative are obtained.

The product obtained in the crude state has been used as such, without additional purification, in the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide by cyclization.

(b) Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

54 g of the crude product obtained in (a) above are dissolved in 125 ml of toluene in the presence of 2 g of 2-hydroxypyridine. The mixture is heated at 110° C. for 12 hours.

The insoluble matter is filtered off hot and the filtrate is then evaporated under reduced pressure.

The residue is purified by chromatography on a column of 1.1 kg of silica (column diameter: 5 cm; eluent: a mixture of ethyl acetate, methanol and concentrated ammonia solution in a proportion by volume of 85:12:3).

The product isolated is recrystallized from 50 ml of ethyl acetate to obtain 17.5 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

Melting point: 117° C.
$[\alpha]_D^{25}$: −90.0° (c = 1, acetone).
Yield: 41%.

## EXAMPLE 3

(a) Preparation of
(S)-N-[1-(aminocarbonyl)propyl]-4-chloro-butanamide

345.6 g (2.5 moles) of ground potassium carbonate are mixed with 138.5 g (1 mole) of (S)-2-amino-butanamide hydrochloride in 2.5 liters of acetonitrile. The reaction mixture is cooled to 0° C. and a solution of 129.2 g (1.2 mole) of 4-chlorobutyryl chloride in 500 ml of acetonitrile is introduced dropwise. After the addition, the reaction mixture is allowed to return to ambient temperature; the insoluble matter is filtered off and the filtrate evaporated under reduced pressure. The crude residue obtained is stirred in 1.2 liter of anhydrous ether for 30 minutes at a temperature between 5° and 10° C. The precipitate is filtered off, washed twice with 225 ml of ether and dried in vacuo to obtain 162.7 g of (S)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide.

Melting point: 118°-123° C.
$[\alpha]_D^{25}$: −18° (c = 1, methanol).
Yield: 78.7%.

The crude product thus obtained is very suitable for the cyclization stage which follows. It can however be purified by stirring for one hour in anhydrous ethyl acetate.

Melting point: 120°-122° C.
$[\alpha]_D^{25}$: −22.2° (c = 1, methanol).

(b) Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

6.2 g (0.03 mole) of (S)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanami and 0.484 g (0.0015 mole) of tetrabutylammonium bromide are mixed in 45 ml of dichloromethane at 0° C. under a nitrogen atmosphere. 2.02 g (0.036 mole) of potassium hydroxide powder are added over 30 minutes, at such a rate that the temperature of the reaction mixture does not exceed −2° C. The mixture is then stirred for one hour, after which a further 0.1 g (0.0018 mole) of ground potassium hydroxide is added and stirring continued for 30 minutes at 0° C. The mixture is allowed to return to ambient temperature. The insoluble matter is filtered off and the filtrate is concentrated under reduced pressure. The residue obtained is recrystallized from 40 ml of ethyl acetate in the presence of 1.9 g of 0.4 nm molecular sieve. The latter is removed by hot filtration to give 3.10 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide. Melting point: 116.7° C.
$[\alpha]_D^{25}$: −90.1° (c = 1, acetone).
Yield: 60.7%.

## EXAMPLE 4

Preparation of
(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

This example illustrates a variant of the process of Example 3, in which the intermediate 4-chlorobutanamide obtained in situ is not isolated. 84 g of anhydrous sodium sulfate are added to a suspension of 69.25 g (0.5 mole) of (S)-2-amino-butanamide hydrochloride in 600 ml of dichloromethane at ambient temperature. The mixture is cooled to 0° C. and 115 g of ground potassium hydroxide are added, followed by 8.1 g (0.025 mole) of tetrabutylammonium bromide dissolved in 100 ml of dichloromethane. A solution of 77.5 g of 4-chlorobutyryl chloride in 100 ml of dichloromethane is added dropwise at 0° C., with vigorous stirring. After 5 hours' reaction, a further 29 g of ground potassium hydroxide are added. Two hours later, the reaction mixture is filtered over Hyflo-cel and the filtrate evaporated under reduced pressure. The residue (93.5 g) is dispersed in 130 ml of hot toluene for 45 minutes. The resultant mixture is filtered and the filtrate evaporated under reduced pressure. The residue (71.3 g) is dissolved hot in 380 ml of ethyl acetate to which 23 g of 0.4 nm molecular sieve in powder form are added. This mixture is heated to reflux temperature and filtered hot. After cooling the filtrate, the desired product crystallizes to give 63 g of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

Melting point: 117° C.
$[\alpha]_D^{25}$: −91.3° (c = 1, acetone).
Yield: 74.1%.

## PHARMACOLOGICAL TESTS

Racemic alpha-ethyl-2-oxo-1-pyrrolidineacetamide (compound A) and (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide (compound B) of the present invention were subjected to pharmacological tests.

1. Protection against hypoxia (mouse)

a. Principle (C. GIURGEA and F. MOURAVIEFF-LESUISSE; Proc. Xth Intern. Congr. of the Coll. Intern. Neuro-psych.-Pergamon Press, Oxford and New York, 1978, p. 1623–1631).

The principle of this test lies in measuring the possibilities of survival of the organism subjected to an atmosphere in which the oxygen level is progressively decreased. Due to the particular sensitivity of the nervous system to this type of aggression, the results obtained in this test can be interpreted as a measure of the resistance of the central nervous system. Compounds which increase the resistance of the animals to this stress are suitable for the treatment and prevention of hypoxic type aggressions of the central nervous system.

b. Method.

The apparatus consists of an airtight transparent cage 37 cm high, 39 cm deep and 97 cm wide. This 140 liter cage is provided with 60 transparent compartments each 6×10×10 cm, making it possible to separately accomodate 60 mice.

A fan ensures circulation of the atmosphere between the compartments through a grid floor. The cage is equipped with a device for introducing nitrogen at a constant flow rate, and with an orifice communicating with the ambient atmosphere. Male mice (*NMRI* strain) weighing 20 to 22 g, are kept fasting as from the day before the test. The experiment is effected on the following day, simultaneously on 3 groups of 20 mice: a control group is given water (25 ml/kg) orally, and the other two groups are each given orally a compound to be tested.

25 minutes after the administration, the animals are distributed at random amongst the compartments so that none of the three groups is concentrated in a preferred area of the cage.

30 minutes after administration, the cage is closed and nitrogen is admitted into it at a constant flow rate (7.75 liters of technical grade nitrogen per minute) for about 37 minutes, at which stage the atmosphere contains 3.7% oxygen.

The cage is left closed until the critical moment where no more than 3 survivors are observed among the 20 control animals. At that moment, the cage is opened and atmospheric air admitted into it. A few moments later the survivors in each group of animals are counted.

For each dose of compound to be tested, the experiments are repeated once or twice, and the results pooled to obtain a minimum of 40 (or 60) animals treated per dose and 40 (or 60) corresponding control animals.

For each dose of compound tested, the number of surviving animals among those treated with the compound is compared with the number of surviving animals among the control animals. The difference between these numbers expresses the protective activity of the compound against hypoxia caused by oxygen deprivation. The statistical significance (P) of this difference is evaluated by the Fischer-Yates test.

c. Results.

Table I below gives the results obtained for increasing doses of compounds A and B.

TABLE I

| Compound tested | Oral dose in mmol/kg | Number of surviving animals: control | treated | P |
|---|---|---|---|---|
| A | 0.032 | 12/60 | 16/60 | NS |
| | 0.1 | 8/60 | 7/60 | NS |
| | 0.16 | 12/60 | 12/60 | NS |
| | 0.32 | 10/60 | 30/60 | <0.001 |
| B | 0.016 | 5/40 | 11/40 | NS |
| | 0.032 | 8/40 | 17/40 | <0.6 |
| | 0.1 | 6/40 | 19/40 | <0.005 |
| | 0.16 | 6/40 | 19/40 | <0.005 |
| | 0.32 | 5/40 | 17/40 | <0.01 |

NS = [illegible]

d. Conclusions.

In this test, the laevorotatory enantiomer of the invention (compound B) increases the survival of the animals deprived of oxygen when administered at doses from 0.032 mmol/kg upwards. The racemate (compound A) exerts a similar activity only from 0.32 mmol/kg upwards (1st effective dose). Thus, the laevorotatory enantiomer of the present invention is 10 times more active than the corresponding racemate.

II. Protection against cerebral ischemia (rats)

a. Principle (C. GIURGEA and F. MOURAVIEFF-LESUISSE: see above under Ia.

Electroencephalographic controls have shown that the ligature of the 2 common carotids in the rat causes a true cerebral ischemia: the electroencephalogram trace flattens and even becomes isoelectric (electric silence).

b. Method.

Male Wistar rats weighing between 250 and 350 g are anesthetized with pentobarbital administered intraperitoneally at a dose of 50 mg/kg (0.5 ml/100 g).

Immediately after the anesthesia, the animals are administered intraperitoneally with an amount of 0.5 ml/100 g, either the compound to be tested dissolved in an isotonic sodium chloride solution (treated animals), or only an isotonic sodium chloride solution or placebo (control animals). About 20 minutes later, the 2 common carotids are exposed and about 10 minutes later ligatured simultaneously. This operation is effected simultaneously on the control animals and the treated animals.

An hour after administration of the compound to be tested or of the placebo, there is again administered intraperitoneally the same dose of either the compound to be tested (to the treated animals) or the placebo (to the control animals).

5 hours after the first administration, there is administered for the third time the same dose of either the compound to be tested (to the surviving treated animals) or the placebo (to the surviving control animals). 24 hours after the first administration the efficacy of the ligature is verified in all animals, under pentobarbital anesthesia, by section of the carotids downstream of the ligature. The number of surviving animals is recorded among both the treated animals and the control animals. For each dose of compound tested, the number of surviving animals among those treated with the compound is compared with the number of surviving animals among the control animals. The difference expresses the protective activity of the compound against the lethality induced by the simultaneous ligature of the 2 carotids. The statistical significance (P) of this difference is evaluated by the Brandt-Snedecor test.

c. Results.

Table II below gives the results obtained for increasing doses of compounds A and B.

TABLE II

| Compound tested | Intraperitoneal dose in mmol/kg | Number of surviving animals: control | treated | P |
|---|---|---|---|---|
| A | 0.32 | 6/29 | 8/29 | NS |
| | 0.64 | 11/30 | 21/30 | 0.01 |
| B | 0.1 | 9/29 | 14/29 | NS |
| | 0.16 | 6/29 | 14/30 | 0.05 |
| | 0.32 | 8/30 | 19/29 | 0.01 |

NS = [illegible]

d. Conclusions.

Table II shows that the racemate (compound A) is only active from a dose of 0.64 mmol/kg upwards. In contrast, the laevorotatory enantiomer of the invention (compound B) protects the animals from 0.16 mmol/kg upwards, against the lethality induced by the simulta-

geous ligature of the two carotids and thus proves to be 4 times more active than the racemate.

III. Toxicity.

Table III below gives, for compounds A and B, the $LD_{50}$ in mg/kg, determined on the male mouse and the male rat after intravenous administration:

TABLE III

| Compound tested | $LD_{50}$ in mg/kg | |
|---|---|---|
| | mouse | rat |
| A | 1790 | 1500 |
| B | 1081 | 1034 |

As can be seen from this table the laevorotatory enantiomer of the invention (compound B) has, like the racemate (compound A), very low toxicity and the toxic dose is well above the active dose.

The compound of the present invention can be administered either orally in the form of solid or liquid compositions for example, in the form of tablets, pills, dragees, gelatine capsules, solutions or syrups, or parenterally in the form of injectable solutions or suspensions.

Pharmaceutical forms such as solutions or tablets are prepared according to conventional pharmaceutical methods. The compound of the invention may be mixed with a solid or liquid non-toxic pharmaceutically acceptable carrier and optionally with a dispersant, a stabilizer and where necessary, colorants and sweeteners.

Similarly the solid or liquid pharmaceutical carriers used in these compositions are well known.

Solid pharmaceutical excipients for the preparation of tablets or capsule include, for example, starch, talc, calcium carbonate, lactose, sucrose and magnesium stearate.

The percentage of active product in the pharmaceutical compositions can vary within very wide limits depending upon the mode of administration and the condition of the patient. The human posology can vary between 250 mg and 3 g per day.

There is given below a non-limiting example of a composition containing the compound of the invention i.e. a 100 mg gelatine capsule for oral administration:

compound B: 100 mg
avicel (microcrystalline cellulose): 217 mg
Mg stearate: 5 mg

We claim:

1. A pharmaceutical composition comprising a therapeutically effective amount of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide and a pharmaceutically acceptable solid or liquid diluent or carrier therefor, said composition being substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

2. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, prepared by the process which comprises cyclizing, in an inert solvent and in the presence of a basic substance, an (S)-2-amino-butanamide of the formula

$$X—CH_2CH_2—Y—NHCHIC_2H_5)CONH_2$$

in which

X represents ZOOC— or $HalCH_2$—, wherein Z is alkyl of 1 to 4 carbon atoms and Hal a halogen atom, and

Y represents $—CH_2—$ or —CO—,

with the proviso that Y is $—CH_2—$ when X represents ZOOC—, and Y is —CO— when X represents $HalCH_2$—.

* * * * *

the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MIFEPREX is 2,249 days. Of this time, 593 days occurred during the testing phase of the regulatory review period, while 1,656 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) became effective:* The applicant claims August 3, 1994, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was August 4, 1994, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505 of the act:* March 18, 1996. FDA has verified the applicant's claim that the new drug application (NDA) for MIFEPREX (NDA 20–687) was initially submitted on March 18, 1996.

3. *The date the application was approved:* September 28, 2000. FDA has verified the applicant's claim that NDA 20–687 was approved on September 28, 2000.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,825 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written or electronic comments and ask for a redetermination by March 26, 2002. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by July 24, 2002. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above) in three copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 14, 2001.

**Jane A. Axelrad,**

*Associate Director for Policy, Center for Drug Evaluation and Research.*

[FR Doc. 02–1926 Filed 1–24–02; 8:45 am]

BILLING CODE 4160–01–S

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 00E–1346]**

### Determination of Regulatory Review Period for Purposes of Patent Extension; KEPPRA

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) has determined the regulatory review period for KEPPRA and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

**ADDRESSES:** Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

**FOR FURTHER INFORMATION CONTACT:** Claudia Grillo, Office of Regulatory Policy (HFD–007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

**SUPPLEMENTARY INFORMATION:** The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product KEPPRA (Levetiracetam). KEPPRA is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for KEPPRA (U.S. Patent No. 4,943,639) from UCB Societe Anonyme, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated May 3, 2001, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of KEPPRA represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for KEPPRA is 2,010 days. Of this time, 1,707 days occurred during the testing phase of the regulatory review period, while 303 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) became effective:* June 1, 1994. The applicant claims May 3, 1994, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 1, 1994, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505 of the act:* February 1, 1999. FDA has

verified the applicant's claim that the new drug application (NDA) for KEPPRA (NDA 21–035) was initially submitted on February 1, 1999.

3. *The date the application was approved*: November 30, 1999. FDA has verified the applicant's claim that NDA 21–035 was approved on November 30, 1999.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,155 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written or electronic comments and ask for a redetermination by March 26, 2002. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by July 24, 2002. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above) in three copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 28, 2001.

**Jane A. Axelrad,**

*Associate Director for Policy, Center for Drug Evaluation and Research.*

[FR Doc. 02–1927 Filed 1–24–02; 8:45 am]

BILLING CODE 4160–01–S

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### Anti-Infective Drugs Advisory Committee; Notice of Meeting

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

*Name of Committee*: Anti-Infective Drugs Advisory Committee.

*General Function of the Committee*: To provide advice and recommendations to the agency on FDA's regulatory issues.

*Date and Time*: The meeting will be held on February 19, 2002, from 8 a.m. to 5:30 p.m. and on February 20, 2002, from 8 a.m. to 4 p.m.

*Location*: Holiday Inn, The Ballrooms, Two Montgomery Village Ave., Gaithersburg, MD.

*Contact*: Tara P. Turner, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301–827–7001, e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12530. Please call the Information Line for up-to-date information on this meeting.

*Agenda*: On February 19, 2002, the committee will hear presentations on the proposed approach for selection of delta in noninferiority (equivalence) clinical trials. The impact of this approach on studies of anti-infective drug products will be considered, with a focus on acute exacerbation of chronic bronchitis and hospital-acquired-pneumonia. On February 20, 2002, the committee will discuss approaches to the development of antimicrobial agents for the treatment of resistant pathogens.

*Procedure*: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by February 11, 2002. Oral presentations from the public will be scheduled between approximately 1 p.m. and 1:30 p.m. on both days. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before February 11, 2002, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: January 16, 2002.

**Linda A. Suydam,**

*Senior Associate Commissioner.*

[FR Doc. 02–1814 Filed 1–24–02; 8:45 am]

BILLING CODE 4160–01–S

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### Oncologic Drugs Advisory Committee; Notice of Meeting

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

*Name of Committee*: Oncologic Drugs Advisory Committee.

*General Function of the Committee*: To provide advice and recommendations to the agency on FDA's regulatory issues.

*Date and Time*: The meeting will be held on February 27, 2002, from 8 a.m. to 5:30 p.m.

*Location*: Holiday Inn, Versailles Ballroom, 8120 Wisconsin Ave., Bethesda, MD.

*Contact*: Karen M. Templeton-Somers, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7001, e-mail: SomersK@cder.fda.gov, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12542. Please call the Information Line for up-to-date information on this meeting.

*Agenda*: The committee will discuss: (1) Trial design considerations and appropriate patient populations for studies of investigational agents for adjuvant therapy of melanoma given the availability of an approved agent for this indication; and (2) the appropriate study design and control for the proposed phase 3 trial of investigational new drug (IND) 2885, MELACINE (melanoma vaccine), Corixa Corp., for adjuvant treatment of melanoma.

*Procedure*: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by February 20, 2002. Oral presentations from the public will be scheduled between approximately 8:15 a.m. and 8:45 a.m., and 1:15 p.m. and 1:45 p.m. Time allotted for each

EXCLUSIVITY SUMMARY for NDA # 21-505 SUPPL # _____
Trade Name Keppra Oral Solution Generic Name Levetiracetam
Applicant Name UCB Pharma HFD- 120
Approval Date 7/15/03

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__x_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__/ NO /_x/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      This application only contained a BE study of the tablet versus liquid formulation

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

      YES /___/ NO /_x/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_/ NO /_x__/

If yes, NDA # Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-035 (Keppra Tablets)

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_x/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Melina Griffis 8/5/03
Signature of Preparer Date
Title: Sr. Regulatory Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Russell Katz

8/5/03 02:23:44 PM

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

## DEBARMENT CERTIFICATION STATEMENT

UCB Pharma, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

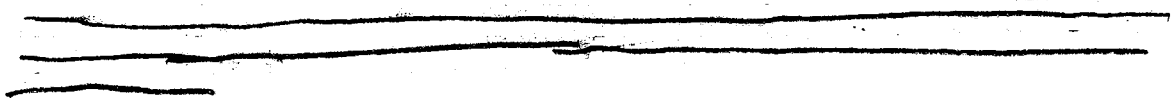
Dan Nall
Vice President, Quality Assurance

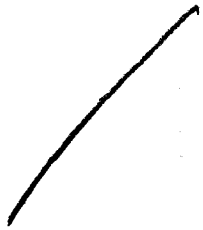
Tel. (770) 437-5500

## 20. LEVETIRACETAM (KEPPRA® ORAL SOLUTION (100 MG/ML) PEDIATRIC DEFERRAL

UCB Pharma, Inc. is requesting a deferral of pediatric studies for NDA #21-505 for Keppra® (levetiracetam) oral solution (100 mg/ml) in accordance with 21 CFR 314.55(b). We have completed and included the Request for Deferral of Pediatric Studies
Section 1 Vol. 9 pg. 1 from the "Guidance: Recommendation for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))."

Keppra® Tablets (250 mg, 500 mg, and 750 mg) are approved under NDA #21-035 for the indication of adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Keppra® Tablets are bioequivalent to Keppra® Oral Solution (100 mg/ml). UCB Pharma, Inc. is requesting a deferral for all pediatric age groups for NDA #21-505 for Keppra® Oral Solution (100 mg/ml) in accordance with 21 CFR 314.55(b) for the indication of adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.





Based on this information, UCB Pharma, Inc. is requesting a deferral for all pediatric age groups for NDA #21-505.

**Table 20:1 Studies**

| Study Number/ Design | Population | Objective | Dosage and Dosage Form | Duration of Study (Status) LPLV[a] |
|---|---|---|---|---|
| **Clinical Pharmacology Studies in Pediatric Epilepsy Patients (Ages** | | | | |
| N151 – Multicenter, Open-Label Pharmacokinetic | 24 Pediatric Epileptic Patients with Partial Onset Seizures | Pharmacokinetic, Efficacy, and Safety | 20 and 40 mg/kg/day<br>Tablets | 22 Weeks (completed) |

3 Page(s) Withheld

24 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | |
|---|---|
| [redacted] | Principal Investigator |
| [redacted] | Subinvestigator |
| [redacted] | Nurse Practitioner |

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| Patricia A. Fritz | Vice President, Regulatory Affairs |
| FIRM/ORGANIZATION: UCB Pharma, Inc. | |
| SIGNATURE: Patricia A. Fritz | DATE: 4-30-02 |

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## Griffis, Melina

| | |
|---|---|
| ·m: | Feeney III, John J |
| ·t: | Friday, July 11, 2003 3:17 PM |
| o: | Griffis, Melina |
| **Cc:** | Hershkowitz, Norman |
| **Subject:** | Memo to File for Keppra |

Melina,

I talked with Patricia Fritz, VP, Reg Affairs at UCB, this afternoon. She (after discussion with her team) agreed to expand the mailing list for the Dear HCP letter to include all neurologists, internists, family practitioners, and basically all primary care physicians. She also agreed to the one change in the PPI...the sentence about not chewing or crushing the tablets will revert to the way it was previously, taking out the statement about the [redacted].

I also informed her that the action letter will include an outline of additional steps for consideration pertinent to name confusion.

APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM**

**NDA 21-505 Keppra Oral Solution 100mg/mL**

**FROM:** John Feeney, M.D.
Neurology Team Leader

**SUBJECT:** New Dosage Form

**DATE:** April 16, 2003

Keppra is currently marketed in the United States as a tablet, available in 3 doses, 250mg, 500mg, and 750mg. At the time of approval, the NDA safety database included 3339 patients (3362 with the safety update) with a data-cutoff of November 30, 1998. The current application is for an oral solution, an alternative for adult patients with difficulty swallowing. In addition, the sponsor has presented new information bearing on the proposed mechanism of action and new safety data. There exist 3247 newly exposed individuals since the last safety update.

**Safety**

Dr. Norman Hershkowitz has reviewed the new safety data provided by the sponsor. Clinical trials safety data included information on 2266/3247 newly exposed individuals with a data-cutoff of December 1, 2001. The sponsor also summarized postmarketing safety data.

The sponsor also provided an analysis of safety data for patients (in the previous NDA safety database) who have continued in open-label extension studies for partial onset seizures. This analysis examines only the subset of patients in these studies who have drug exposure time of 6 months or greater, n=1036.

Also included is a postmarketing study conducted by the sponsor. UCB surveyed German patients who received Keppra for at least a 9-month period, n=774.

Finally, the sponsor provided a literature review.

*Deaths*

Seven new deaths are described but none of them represent unexpected events that would require a labeling change.

*Serious Adverse Events*

No unexpected events are described.

*Dose Reduction/Discontinuation*

No unexpected pattern of adverse events leading to dose reduction/discontinuation was identified during the review process.

*AEs of Interest*

Hematologic—The division has been aware of 4 cases of concerning pancytopenia associated with Keppra, 2 domestic and 2 foreign. No new information about these cases or similar cases is presented in this submission. Dr. Hershkowitz does not believe changes to labeling are warranted at this time.

Hepatic Function—There is one new report of hepatic encephalopathy leading to death, but this case is attributed to alcohol induced cirrhosis.

Renal—Dr. Hershkowitz describes 2 cases of renal pathology associated with Keppra, but in both cases there are alternative possible explanations for the findings. Dr. Hershkowitz recommends no label change at this time. Because of a high percentage of abnormalities of urinalysis noted in the analysis of patients treated for 6 months or greater, he does believe the sponsor should be asked to further analyze these cases; they may be attributable to the occurrence of urinary tract infections over the long period of study.

Skin Reactions—No new serious skin reactions are reported. Dr. Hershkowitz does describe several apparently-allergic rashes.

**Nomenclature**

With the introduction of a new dosage form, the Division of Medication Errors and Technical Support (DMETS) re-reviewed the product name and its potential for confusion with other products and found potential confusion between Keppra and Kaletra. Kaletra is a combination, anti-HIV product also available as an oral solution.

There are currently reports of several dispensing errors involving confusion between Keppra and Kaletra. Fortunately, these errors were noted before patients took the wrong medication. DMETS anticipates that the likelihood for dispensing errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. This is likely because orders such as "Keppra 5mL PO BID" and "Kaletra 5mL PO BID" are both within the usual dosing for each product.

Therefore, the sponsor should be asked to develop a plan to minimize this risk. As a starting point, DMETS proposed the following:

- Consider using a highlighted area or font style to emphasize the letters in the middle of the name that differ from Kaletra.

- Consider a "Dear Healthcare Practitioner" letter to alert practitioners to the potential for errors between Keppra and Kaletra.

The clinical review team would also asked the sponsor to alert patients to the potential confusion by directly addressing the problem in the Patient Package Insert (PPI).

**Inspections**

DSI performed inspections of 1 clinical site and 1 analytical site. Data was deemed reliable.

**Chemistry**

Dr. Broadbent performed the chemistry review and recommended an Approval action.

**Pharm/Tox**

Dr. Fisher has reviewed the sponsor's proposed labeling changes under Mechanism of Action. He has provided changes to the sponsor's proposals.

**Bioequivalence Studies**

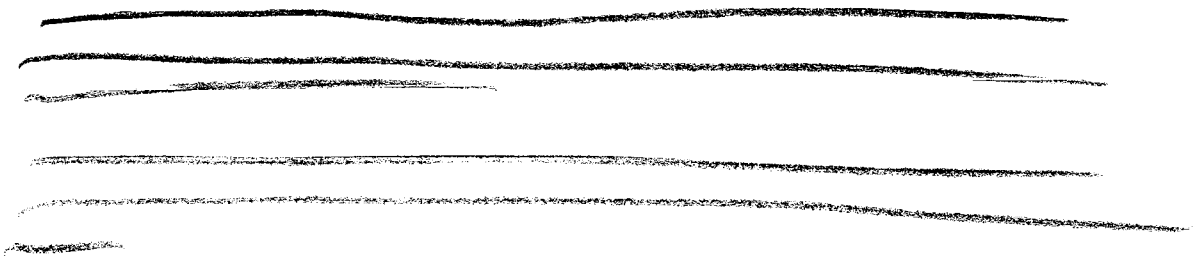
Dr. Kumi reviewed the bioequivalence data and found the products bioequivalent. New labeling changes describing drug-drug interactions were also deemed acceptable. Of note, some of these labeling changes are supported by studies reviewed with the original NDA.

**Labeling**

The sponsor has proposed a novel addition to labeling, [redacted]. Based on analyses provided in this submission, the sponsor wishes to state, [redacted]

Dr. Hershkowitz has reviewed the analyses provided in support of this proposed labeling change. The following limitations of these analyses have been identified:

[redacted]



For these reasons, I do not believe these analyses should be reflected in labeling. The sponsor's proposal has been deleted from our draft labeling.

**Conclusions**

The new oral solution is Approvable. An Approval action is not possible now for 2 reasons. First, the division, with help from our consultants, has proposed extensive changes to the sponsor's proposed labeling/PPI. The sponsor has not yet seen these proposed changes. Second, because of concerns about dispensing errors with Kaletra, the sponsor should develop plans to minimize this risk *prior to marketing*.

**Recommendations**

The sponsor should be sent an Approvable letter with labeling.

**CONSULTATION RESPONSE**
**Division Of Medication Errors And Technical Support**
**Office Of Drug Safety**
**(DMETS; HFD-420)**

| DATE RECEIVED: AUG-6-2002 | DUE DATE: APRIL-8-2003 | ODS CONSULT: 02-0167 |
|---|---|---|

**TO:**

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

**THROUGH:**

Melina Griffis
Project Manager
HFD-120

| PRODUCT NAME: | NDA SPONSOR: |
|---|---|
| Keppra<br>(Levetiracetam Oral Solution)<br>100 mg/mL<br><br>NDA #: 21-505 | UCB Pharma |

**SAFETY EVALUATOR:** Marci Lee, PharmD

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Keppra" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

1. DMETS anticipates that the likelihood for errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. DMETS recommends the sponsor implement a risk management plan to address this potential increased risk.

2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**HFD-420; Parklawn Rm. 6-34**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** April 2, 2003

**NDA NUMBER:** 21-505

**NAME OF DRUG:** Keppra (Levetiracetam Oral Solution) 100 mg/mL

**NDA SPONSOR:** UCB Pharma

## I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the tradename "Keppra", regarding potential name confusion with other proprietary/generic drug names.

The proprietary name, Keppra, was found acceptable by DMETS in consult 99-046, dated NOV-9-1999. NDA 21-035 for Keppra (Levetiracetam Tablets) was approved on NOV-30-1999. The sponsor is now proposing to use the name Keppra for the oral solution formulation. The labels and labeling for Keppra Oral Solution were also submitted for DMETS to review.

PRODUCT INFORMATION

Keppra Oral Solution is indicated for adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Treatment should be initiated at 500 mg by mouth twice daily. The maximum recommended daily dose is 3000 mg per day. Keppra can be administered with or without food. Keppra Oral Solution will be available as a clear, dye-free, grape-flavored liquid for oral administration. The concentration of Keppra will be 100 mg/mL. Keppra tablets are available as 250 mg, 500 mg and 750 mg.

## II. RISK ASSESSMENT

Since Keppra is already marketed, DMETS did not conduct prescription simulation studies to assess the name for potential look-alike and sound-alike name confusion. In addition, the DMETS Expert Panel did not evaluate Keppra for potential confusion at this time. These processes were incorporated into the original review of Keppra for the tablet formulation in November 1999.

### A. ADVERSE EVENT REPORTING SYSTEM (AERS)

The DMETS medication error staff conducted a search of the Adverse Event Reporting System (AERS) to identify any reports of medication errors associated with Keppra Tablets. A review of these medication error reports identified that there is confusion potential between Keppra and Kaletra.

The search results included three reports of actual confusion between Keppra and Kaletra. In addition, there was one report of potential confusion. The reports are summarized below.

**ISR # 3895545-7/Date Received by FDA APR-4-2002**
**Actual error report**
**Event date JAN-29-2002**
**IL**
**Patient was discharged from hospital before he received a dose of the wrong drug.**

"A patient was ordered **Keppra** 500 mg every 12 hours but **Kaletra** was dispensed. The brand names sound alike, which probably contributed to the error. The patient was discharged and never received the medication. While cleaning out the refrigerator, a pharmacist found a bag labeled **Keppra** containing a "REFRIGERATE" tag on it. Upon opening the bag, it was noted that it contained Kaletra capsules."

**ISR # 4018780-6/Date Received by FDA DEC-3-2002**
**Actual error report**
**Event date JAN-25-2002**
**Unknown location**
**Patient did not take the medication.**

"Wrong drug labeled. Bottle of **Kaletra** labeled as **Keppra**. Prescription was entered correctly. Wrong drug pulled from stock. Patient fiancé noticed after brought home. Patient's fiancé picked up medication and noticed it was incorrect."

**ISR# 3667800-7/Date Received by FDA FEB-21-2001**
**Actual error report**
**Event date JAN-17-2001**
**CT**
**Patient did not receive wrong medication.**

"A classic look-alike, sound-alike. Physician was trying to identify **Keppra** by asking the (drug information) pharmacist over the phone. The pharmacist thought the physician stated, "**Kaletra**". Almost made wrong recommendation. Drug name was clarified to physician after identifying the patient's medical profile. Pharmacist discovered that the patient did not have HIV."

**ISR# 3667799-3/Date Received by FDA FEB-21-2001**
**Potential error report**
**OH**

"Currently the products are available in different mg strengths and dosage forms but this may not always be the case. Keppra is an anticonvulsant used as adjunctive therapy for adults whose seizures are not controlled by other regimens. Although it is not approved for pediatric patients, it is sometimes used for pediatric patients who do not respond to currently approved medications. **Kaletra** is a recently approved combination product used in conjunction with other antiretrovirals for the treatment of HIV infection. It is approved for use in both adult and pediatric patients."

## B. SAFETY EVAULATOR RISK ASSESSMENT

Based upon the medication error reports, Kaletra and Keppra have potential for look-alike and sound-alike confusion. DMETS acknowledges that these errors occurred despite numerous characteristics that differ between Keppra and Kaletra. See Appendix A for a comparison of Keppra and Kaletra.

Keppra and Kaletra are used to treat different conditions. Although there is no overlap of the dosage strengths, both products are available in oral solid dosage forms (capsule or tablet). Additionally, Kaletra contains two active ingredients while Keppra contains a single active ingredient. Both medications are administered by mouth twice daily.

Another consideration is that Keppra was approved NOV-30-1999 and Kaletra was approved less than one year later on SEPT-15-2000. This may be an example of when there is not enough time for practitioners to become familiar with Keppra and they easily confuse the characteristics of Keppra with Kaletra.

DMETS anticipates that the likelihood for errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. This means that both medications will have an oral liquid formulation that could be ordered by milliliters instead of milligram strengths leading to confusion and errors. Orders such as: "Keppra 5 mL PO BID" and "Kaletra 5 mL PO BID" are both within usual dosing for each.

DMETS plans to complete a post-marketing medication error review and alert the sponsor for Kaletra to this potential confusion as well.

## III. COMMENTS TO THE SPONSOR

Several medication error reports identified that there is confusion potential between Keppra and Kaletra. Based upon these reports, Kaletra and Keppra have potential for look-alike and sound-alike confusion. DMETS acknowledges that these errors occurred despite numerous characteristics that differ between Keppra and Kaletra. See Appendix A for a comparison of Keppra and Kaletra.

Keppra and Kaletra are used to treat different conditions. Although there is no overlap of the dosage strengths, both products are available in oral solid dosage forms (capsule or tablet). Additionally, Kaletra contains two active ingredients while Keppra contains a single active ingredient. Both medications are administered by mouth twice daily.

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DMETS anticipates that the likelihood for errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. This means that both medications will have an oral liquid formulation that could be ordered by milliliters instead of milligram strengths leading to confusion and errors. Orders such as: "Keppra 5 mL PO BID" and "Kaletra 5 mL PO BID" are both within usual dosing for each.

DMETS recommends the sponsor implement a risk management plan to address this increased risk.

- Consider using a highlighted area or font style to emphasize the letters in the middle of the name that differ from Kaletra. See Appendix B for an example of this strategy.

- Consider a "Dear Healthcare Practitioner" letter to alert practitioners to the potential for errors between Keppra and Kaletra.

In review of the container labels, insert labeling and patient information leaflet, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has reviewed the current container labels and insert labeling and has identified several areas of possible improvement, which might minimize potential user error. Carton labeling was not provided for review at this time.

A. GENERAL COMMENTS

In accordance with the Poison Prevention Act, drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 60 mL bottles, should include Child Resistant Closures (CRC). Please ensure the bottles utilize such a closure.

B. CONTAINER LABELS [100 mg/mL – 60 mL (Physician sample) and 473 mL]

1. Modify the established name to read [redacted] This will increase the prominence of the dosage strength information on the label.

2. Consider listing the dosage strength as [redacted] since the usual starting dose is 500 mg twice daily.

## IV. RECOMMENDATIONS

A. DMETS anticipates that the likelihood for errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. DMETS recommends the sponsor implement a risk management plan to address this increased risk.

B. DMETS recommends implementation of the labeling revisions described in Section III.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

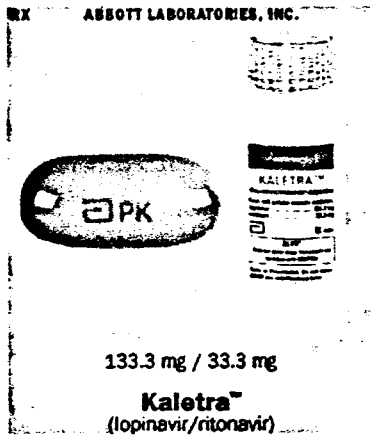
Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

Concur:

/S/

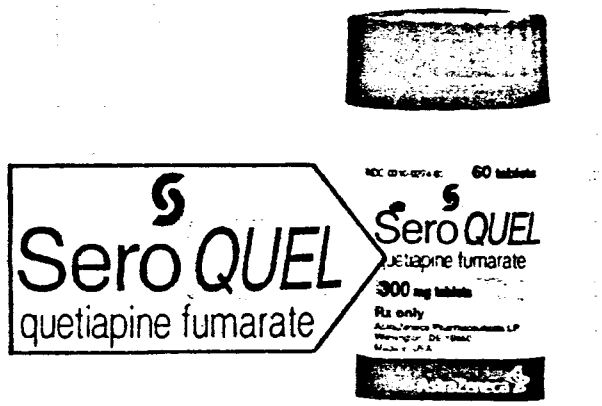
Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

# APPENDIX A – Comparison of Keppra and Kaletra

| Proprietary Name | Keppra | Kaletra |
|---|---|---|
| Established Name | Levetiracetam | Lopinavir/Ritonavir |
| Approval Date | NOV-30-1999 | SEPT-15-2000 |
| Sponsor | UCB Pharma | ABBOTT |
| Indication | Adjunctive therapy in the treatment of partial onset seizures in adults w/epilepsy | HIV infections |
| Patient Population | Adults | Adults and Children |
| Dosage Strength | 250 mg, 500 mg,<br>750 mg<br>*Proposed 100 mg/mL* | 133.3 mg/33.3 mg<br>80 mg/20 mg per mL |
| How Supplied | 100s, 500s, UD 100s<br>*Proposed Oral Solution*<br>*473 mL and 60 mL (sample)* | 180s<br>160 mL bottle with dosing cup<br>  |
| Usual Dose and Range | 500 mg PO BID up to 1500 mg PO BID | 400 mg/100 mg (as 3 capsules or 5 mL) BID with food |
| Frequency of Administration | BID | BID |
| Route of Administration | Oral | Oral |
| Dosage formulation | Tablet<br>*Oral solution* *(Proposed)* | Capsule<br>Oral Solution |
| Storage conditions | Room Temperature | Refrigerate<br>Stable at room temperature for 2 months |

## APPENDIX B – SeroQUEL Example

## Emphasis of letters in part of product name:



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/s/

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