

The [redacted] The results of stability evaluation show that the stability of the analyte was not significantly affected when samples were stored at room temperature for 24 hours or had gone through [redacted] The data demonstrate that the assays of levetiracetam for measurements in plasma and urine provided reliable results.

The assay for ucb L057 is specific and linear over the range [redacted] The LOD and LOQ of this method were [redacted] The coefficient of variations for intra-run and inter-run precision and accuracy were within [redacted] Plasma samples containing ucb L057 were stable at room temperature for 24 hours [redacted] and for 16 months at -20°C. Overall the assays are found to be satisfactory in terms of specificity, sensitivity, linearity, precision and accuracy.

### Levetiracetam (ucb L059) Dissolution Testing

Is the to be marketed tablet (TBM) the same as the clinically studied tablet?  
What is the dissolution method and specification being proposed?  
How are the 250 mg and 750 mg tablets linked to the 500 mg tablets?

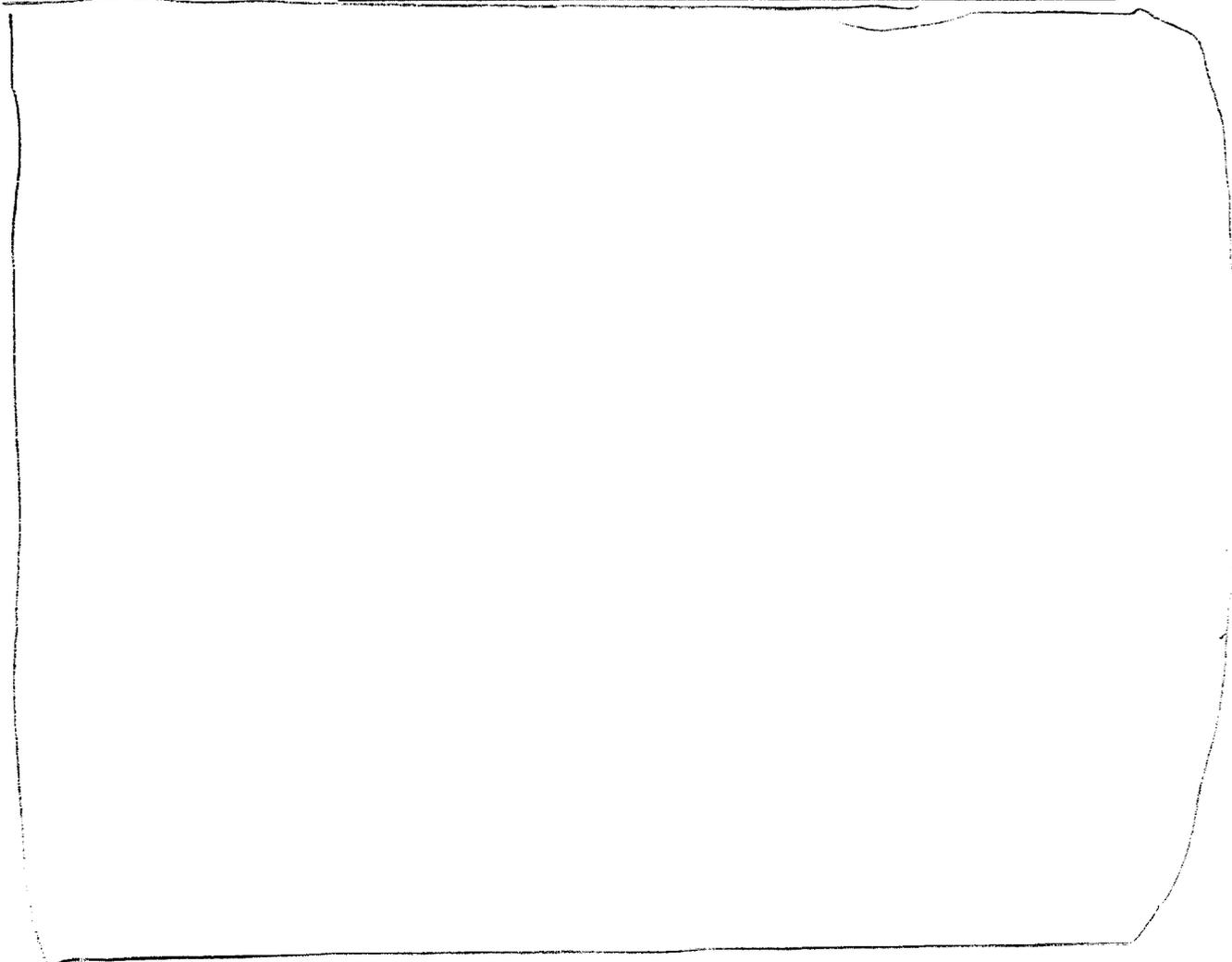


Table 34  
Composition of Proposed Commercial Levetiracetam Tablets

Component	Weight (mg)	Weight (mg)	Weight (mg)
Levetiracetam	250.0	500.0	750.0
Corn starch			
Povidone			
Talc			
Colloidal silicon dioxide			
Magnesium stearate			
Tablet Weight			

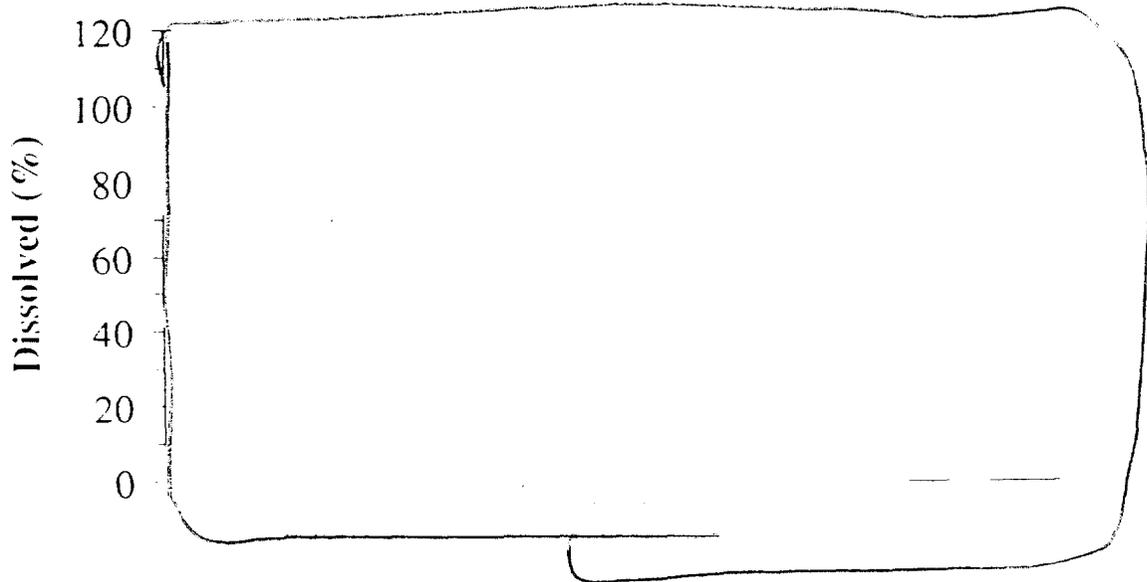
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Table 49  
Multi-media [redacted] Dissolution of 500 mg Levetiracetam White Tablets

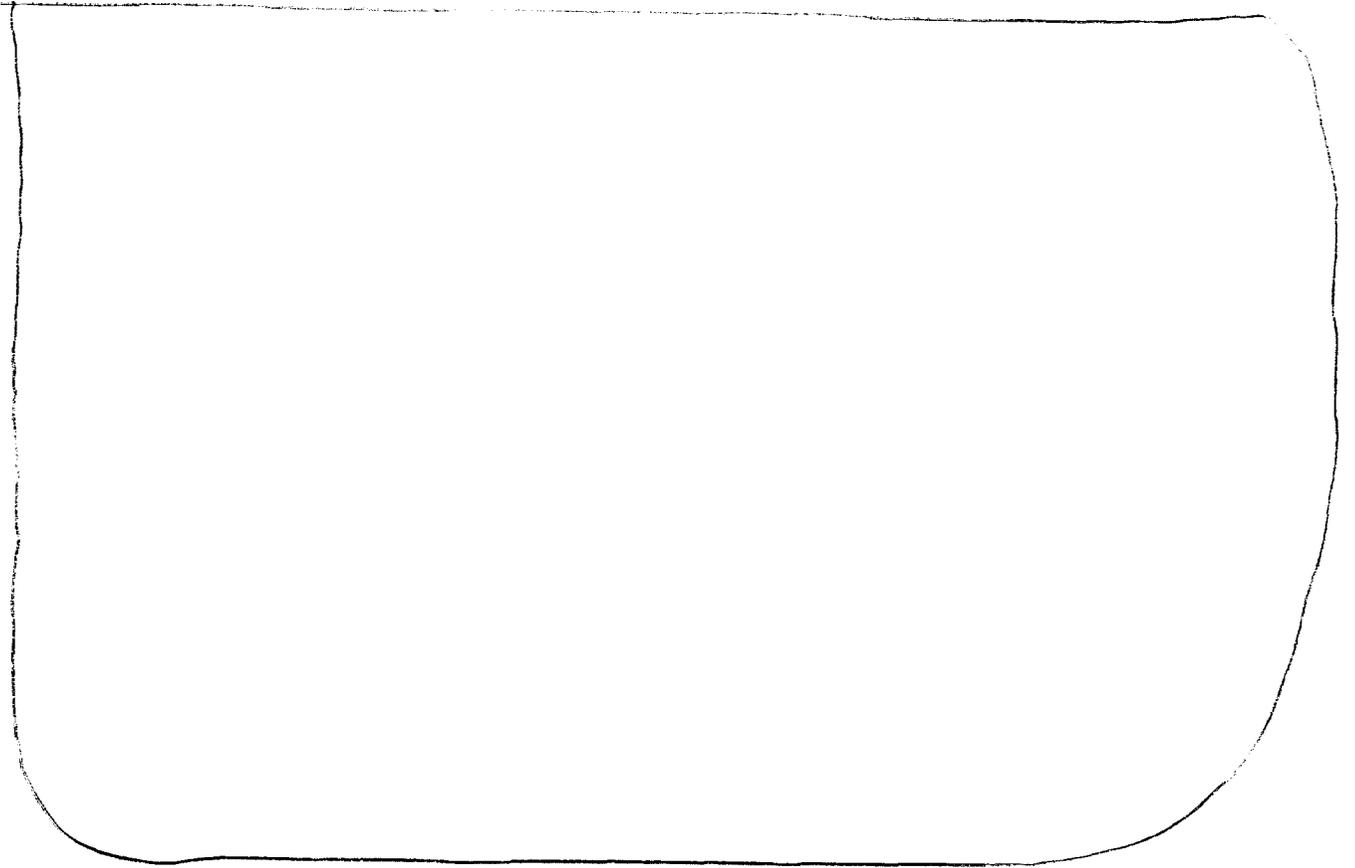
Time	Mean
15 min.	
30 min.	
45 min.	
15 min.	
30 min.	
45 min.	

500 mg white tablets



□ 15 min. ■ 30 min. □ 45 min.

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Primary Reviewer: Hong Zhao, Ph.D.  
OCPB / DPE I

[Redacted] /S/ 3-99

Team Leader: Raman Baweja, Ph.D.

[Redacted] /S/ 11/3/99.

OCPB Briefing on November 1, 1999. Attendees: Drs. Larry Lesko, Shiew-Mei Huang, Mehul Mehta, Tom Oliver, Zak Wahba, Tom Parmelee, Kathleen Uhl, Wendy Chow, Paul Hepp, Glenna Fitzgerald, Mei-Ling Chen, Chanira Sahajwalla, Jennifer Burris, Joel Freiman, Joga Gobburu, Raman Baweja, Hong Zhao.

cc: NDA# 21-035, HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

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Table 4 : Amount of dissolved Levetiracetam (in % of the labeled content)

Labeled content (mg)	250	500	500	500	750
Batch N°					
Color					
Time					

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**ucb Pharma**

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

### 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.

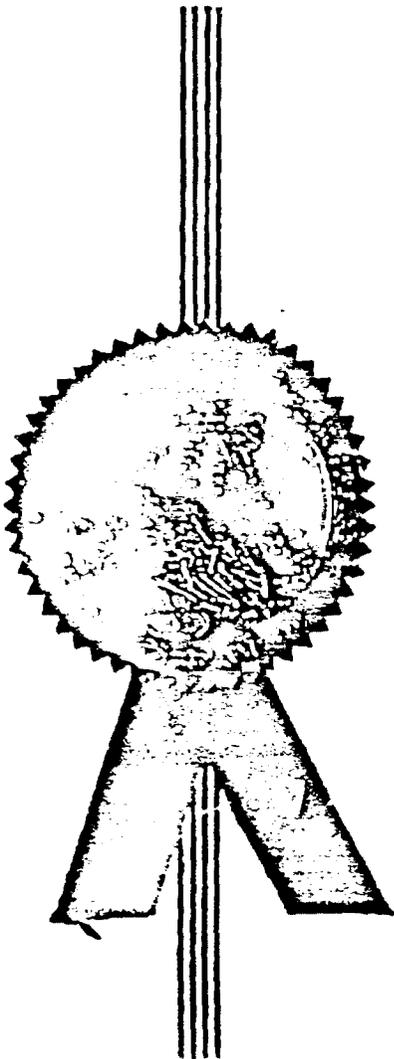
The following patents claim the drug Levetiracetam ((s)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide):

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.

The  
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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 en-  
closed. The requirements of law have  
been complied with, and it has been de-  
termined 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, sub-  
ject 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-PYR-  
ROLIDINEACETAMIDE COMPOSITIONS

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

[73] Assignee: UCB Societe Anonyme, Brussels,  
Belgium

[\*] 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.<sup>4</sup> ..... C07D 207/277; 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

2081508 12/1971 France .  
2368275 5/1978 France .

Primary Examiner—David B. Springer  
Attorney, Agent or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, its prepa-  
ration 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 cycliz-  
ing an (S)-2-amino-butanamide of the formula  
X-CH<sub>2</sub>CH<sub>2</sub>-NHCH (C<sub>2</sub>H<sub>5</sub>)CONH<sub>2</sub> wherein Y is a  
-CH<sub>2</sub>-radical when X represents a ZOOC-radical  
and Y is a -CO- radical when X represents a HalC-  
H<sub>2</sub>-radical, Z being a C<sub>1</sub>-C<sub>4</sub> 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

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**(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, hypertension 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 (antischemia).

As a result of this unexpected combination of properties the levorotatory 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 levorotatory 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:

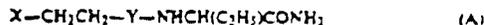
(a) reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with (1) an alkyl haloformate of the formula HalCOOZ in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms and with (2) ammonia. The alkyl haloformate is preferably ethyl chloroformate.

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-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 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



in which

X represents a ZOOC— or HalCH<sub>2</sub>— 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<sub>2</sub>— or —CO— radical.

with the proviso that Y is a —CH<sub>2</sub>— radical when X represents a ZOOC— radical and Y is a —CO— radical when X represents a HalCH<sub>2</sub>— 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<sub>2</sub>—).

When X represents a ZOOC— radical and Y is a —CH<sub>2</sub>— radical the compound of formula A is an alkyl (S)-4-[(1-aminocarbonyl)propyl]amino]butyrate of the formula ZOOCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHCH(C<sub>2</sub>H<sub>5</sub>)CONH<sub>2</sub>, 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Hal in which Z has the meaning given above and Hal is a halogen atom.

When X represents a HalCH<sub>2</sub>— 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CONHCH(C<sub>2</sub>H<sub>5</sub>)CONH<sub>2</sub>, in which Hal has the meaning given above. This latter compound can be prepared by condensing (S)-2-amino-butanamide with a 4-halobutyl halide of the formula HalCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COHal, 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-halobutyl 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  $-5^{\circ}$  to  $+100^{\circ}$  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  $\text{HalCH}_2$  radical and Y a  $-\text{CO}-$  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 ( $\pm$ )-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:  $148^{\circ}$ - $151^{\circ}$  C. Yield: 77.1%.

This salt may be purified by heating under reflux in 48.3 liters of benzene for 4 hours. The mixture is cooled and filtered to obtain 5.040 kg of the desired salt.

Melting point:  $152^{\circ}$ - $153.5^{\circ}$  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  $25^{\circ}$  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:  $125.9^{\circ}$  C.

$[\alpha]_D^{20} = -26.4^{\circ}$  ( $c=1$ , 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  $-30^{\circ}$  C. 24.3 g (0.24 mole) of triethylamine are added dropwise over 15 minutes. The reaction mixture is then cooled to  $-40^{\circ}$  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 4 1/2 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:  $115^{\circ}$ - $118^{\circ}$  C.

$[\alpha]_D^{25} = -89.7^{\circ}$  ( $c=1$ , acetone).

Yield: 72.3%.

Analysis for  $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$  in %: calculated: C 56.45; H 8.29; N 16.46; found: 56.71; 8.22; 16.48;

The racemic ( $\pm$ )-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 ( $\pm$ )-alpha-ethyl-2-oxo-1-pyrrolidineacetate at a temperature not exceeding  $60^{\circ}$  C. When this addition is complete, the temperature of the mixture is raised to  $80^{\circ}$  C. and the alcohol formed is distilled off until the temperature of the reaction mixture reaches  $100^{\circ}$  C.

The reaction mixture is then cooled to  $0^{\circ}$  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 ( $\pm$ )-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, melting at  $155^{\circ}$ - $156^{\circ}$  C., are thus obtained.

Yield: 78%.

Analysis for  $\text{C}_8\text{H}_{14}\text{NO}_2$ , 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 ( $[\alpha]_D^{25} = +26.1^{\circ}$ ;  $c=1$ , methanol) in 400 ml of toluene. The mixture is heated to  $80^{\circ}$  C. and 67.2 g (0.345 mole) of ethyl 4-bromobutyrate are introduced dropwise.

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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-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 hydrox-

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ide 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. 34 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. GURGEA 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.

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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 6x10x10 cm, making it possible to separately accommodate 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 (NMR1 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		P
		control	treated	
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 = statistically non-significant.

#### 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 la-

evorotatory 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 ligation 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 ligation is verified in all animals, under pentobarbital anesthesia, by section of the carotids downstream of the ligation. 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 ligation 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		P
		control	treated	
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 = non-significant difference.

#### 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-

neous ligation  
4 times more

Table II  
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peous ligature of the two carouds 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<sub>50</sub> in mg/kg, determined on the male mouse and the male rat after intravenous administration:

TABLE III

Compound tested	LD <sub>50</sub> in mg/kg	
	mouse	rat
A	1790	1500
B	1081	1031

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, dragées, 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.

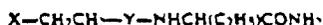
There is given below a non-limiting example of a composition containing the compound of the invention i.e. a 100 mg gelatine capsule for oral administration:

- 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



in which

X represents ZOOC— or HalCH<sub>2</sub>—, wherein Z is alkyl of 1 to 4 carbon atoms and Hal a halogen atom, and

Y represents —CH<sub>2</sub>— or —CO—,

with the proviso that Y is —CH<sub>2</sub>— when X represents ZOOC—, and Y is —CO— when X represents HalCH<sub>2</sub>—.

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*Therefore, this*

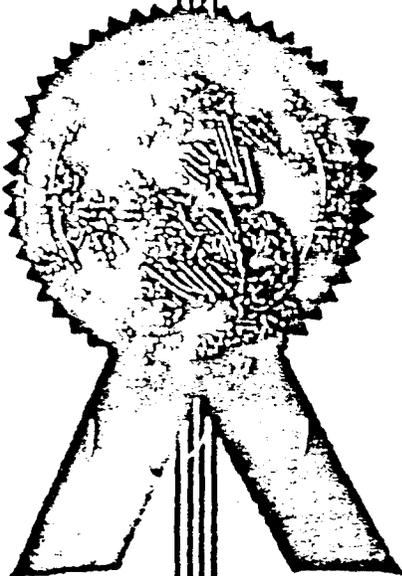
United States Patent

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*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-PYR-  
ROLIDINEACETAMIDE
- [75] Inventors: Jean Gobert, Brussels; Jean-Pierre  
Geertz, Leglise; Guy Bodson,  
Belfontaine, 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. 25,277, 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.<sup>3</sup> ..... C07D 207/277

- [52] U.S. Cl. .... 548/550  
[58] Field of Search ..... 548/546, 550; 514/424

Primary Examiner—David B. Springer  
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, its prepara-  
tion 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 cycliz-  
ing 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  $ZOOC-$  radi-  
cal 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

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**(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, hypertension 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. (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 (anoxypoxia) and
- (2) having a 4 times higher protective activity against ischemia (antiischemia).

As a result of this unexpected combination of properties the levorotatory 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 or 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 levorotatory 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.

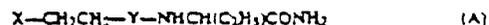
This reaction is generally carried out in dichloromethane at a temperature between -10° and -60° C.

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 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



in which

X represents a ZOOC— or HalCH<sub>2</sub>— 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<sub>2</sub>— or —CO— radical,

with the proviso that Y is a —CH<sub>2</sub>— radical when X represents a ZOOC— radical and Y is a —CO— radical when X represents a HalCH<sub>2</sub>— 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<sub>2</sub>—).

When X represents a ZOOC— radical and Y is a —CH<sub>2</sub>— radical the compound of formula A is an alkyl (S)-4-[[1-(aminocarbonyl)propyl]amino]butyrate of the formula ZOOCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHCH(C<sub>2</sub>H<sub>5</sub>)CONH<sub>2</sub>, 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Hal, in which Z has the meaning given above and Hal is a halogen atom.

When X represents a HalCH<sub>2</sub>— 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CONHCH(C<sub>2</sub>H<sub>5</sub>)CONH<sub>2</sub>, 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<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COHal, 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 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 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<sub>2</sub>- 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 R. 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 48.3 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]<sub>D</sub><sup>20</sup> = -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 mm molecular sieve in powder form.

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

Melting point: 115°-118° C. [alpha]<sub>D</sub><sup>25</sup> = -89.7° (c=1, acetone). Yield: 72.3%.

Analysis for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 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<sub>8</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 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]<sub>D</sub><sup>25</sup>: +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-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 essen-

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dially 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

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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.

## I. 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 6x10x10 cm, making it possible to separately accommodate 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		P
		control	treated	
A	0.032	12/60	16/60	NS
	0.1	8/60	7/60	NS
	0.16	12/60	12/60	NS
B	0.32	10/60	30/60	<0.001
	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 = statistically non-significant.

#### 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 ligation of the 2 common carotids in the rat causes a true cerebral isch-

emia: 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 ligation 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		P
		control	treated	
A	0.32	6/29	8/29	NS
	0.64	11/20	21/20	0.01
B	0.1	9/29	14/29	NS
	0.16	6/29	14/20	0.05
	0.32	8/20	19/29	0.01

NS = non-significant difference.

#### 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 ligation 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<sub>50</sub> in mg/kg, determined on the male mouse and the male rat after intravenous administration:

TABLE III

Compound tested	LD <sub>50</sub> in mg/kg	
	mouse	rat
A	1790	1900
B	1081	1031

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 gelatine capsule for oral administration:

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

We claim:

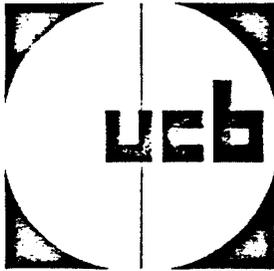
1. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

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.

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**New Drug Application**

**Levetiracetam Film-Coated Tablets  
250 mg, 500 mg, 750 mg**

**Section 14**

**PATENT CERTIFICATION**

21-655

**APPEARS THIS WAY  
ON ORIGINAL**



**Pharma**

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

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**SECTION 14. PATENT CERTIFICATION**

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.

A handwritten signature in black ink, appearing to read 'Patricia A. Fritz', written over a circular stamp.

Patricia A. Fritz  
Director, Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**Exclusivity Summary Form**

Trade Name: **Keppra**

Generic Name: **Levetiracetam**

Applicant Name: **UCB Pharma**

HFD#: **HFD-120**

Approval Date If Known: ~~4/4~~ **11/30/99**

**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 question about the submission.

- a) Is it an original NDA? YES /  / NO /  /
- b) Is it an effectiveness supplement? YES /  / NO /  /  
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 /  /

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.

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 /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?  
**The applicant requested 5 years of marketing exclusivity.**

- e) Has pediatric exclusivity been granted for this Active Moiety? **NO** \_\_\_\_\_

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

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 /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade? YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /  / NO /  /

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

2. Combination product – not applicable

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# \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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."

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 /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

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.

(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 8:

(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:

*Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.*

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 /\_/\_/

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

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 /\_\_\_/

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

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"):

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 /\_\_\_/

If no, explain:

Investigation #2 IND # \_\_\_\_\_ YES /\_\_\_/ NO /\_\_\_/

If 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 IND # YES /\_ \_ \_\_/ NO /\_\_\_/

If no, explain:

Investigation #2 IND # \_\_\_\_\_ YES /\_\_\_/ NO /\_\_\_/

If 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:



### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21035 Trade Name: KEPRA (LEVETIRACETAM) 250/500/750MG TABS

Supplement Number: Generic Name: LEVETIRACETAM

Supplement Type: Dosage Form: Tablet; Oral

Regulatory Action: PN Proposed Indication: Adjunctive therapy in the treatment of partial onset seizures with and without secondary generalization in adults with epilepsy.

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

**What are the INTENDED Pediatric Age Groups for this submission?**

NeoNates (0-30 Days )  Children (25 Months-12 years)

Infants (1-24 Months)  Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups

Formulation Status -

Studies Needed STUDIES needed. Applicant in NEGOTIATIONS with FDA

Study Status Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELINA MALANDRUCCO

 10/25/99

Signature Date



**New Drug Application**

**Levetiracetam Film-Coated Tablets  
250 mg, 500 mg, 750 mg**

**Item 16**

**DEBARMENT CERTIFICATION**



**ucb Pharma**

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

**APPEARS THIS WAY  
ON ORIGINAL**

**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.

A handwritten signature in black ink, appearing to read 'Patricia A. Fritz', written over a faint circular stamp.

Patricia A. Fritz  
Director, Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** November 9, 1999

**FROM:** Glenna G. Fitzgerald, Ph.D.  
Pharmacology Team Leader  
Division of Neuropharmacological Drug Products, HFD-120

**TO:** NDA 21-035  
Kepra™, levetiracetam  
UCB Pharma, Inc.  
250, 500 and 750 mg. Tablets

**SUBJECT:** Approvability for Pharmacology and Toxicology

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Levetiracetam is an analog of the nootropic piracetam, having an ethyl group on the side-chain carbon. It is indicated as adjunctive therapy in the treatment of partial onset seizures with and without secondary generalization in adults with epilepsy. The mechanism for the antiepileptic activity of levetiracetam is unknown. There is no apparent effect on mechanisms which involve inhibitory or excitatory neurotransmission, and it is not active in many of the usual animal models which predict antiepileptic activity. It does display inhibitory effects in kindled rats, both during kindling development and in the fully kindled state. This model is thought to be predictive of effects in human complex partial seizures.

The primary pharmacology and toxicology review of levetiracetam has been prepared by Dr. Jennifer Burris. Others who contributed reviews or had input are Drs. Aisar Atrakchi, J.E. Fisher, Lois Freed, and Barry Rosloff.

In reproductive toxicology studies there was evidence that levetiracetam caused developmental toxicity at doses similar to human therapeutic doses. In rats, doses studied were not associated with maternal toxicity, and higher doses could conceivably have been used. However, in the studies that were conducted there was evidence for skeletal abnormalities, retarded pup growth, increased pup mortality and behavioral alterations at a dose which was only 6 times the recommended maximum daily human dose on a mg/m<sup>2</sup> basis. The no-effect dose was only a fraction of the maximum human dose. Maternal toxicity was achieved in rabbits; however, effects were seen at non-toxic doses as well as at maternally toxic doses, including increases in embryofetal mortality, skeletal abnormalities and retarded growth of offspring. At the maternally toxic dose there was also increased pup mortality and behavioral alterations. The no-effect dose in that species was approximately equivalent to the maximum daily human dose on a mg/m<sup>2</sup> basis.

An issue arose during the review of this NDA when the FDA was notified by the sponsor on July 16, 1999 that the European Agency for the Evaluation of Medicinal Products (EMEA) had suspended review of the application. The primary reason for this action was that drug levels were found in plasma from control animals in the 13-week mouse dose-ranging study and both mouse and rat carcinogenicity studies. There were also several other less serious issues (see pages 23 - 24 of Dr. Burris' review). Inspections and audits were conducted by both UK (where the studies were conducted) and Belgian (where the plasma was analyzed) GLP Monitoring Authorities. It was determined that the studies were conducted according to GLP with only minor deviations, although the cause for the contamination was not determined. The FDA was notified on September 30, 1999 that the EMEA had resumed their review. The sponsor is independently conducting a peer review of the rat carcinogenicity study and will repeat the statistical analysis of tumors. That report has not yet been received and should be requested for submission as soon as it is available. It is expected that the work will be completed this month.

The rat and mouse dietary carcinogenicity studies were taken to the CDER Carcinogenicity Assessment Committee - Executive Committee (CAC - EC) on September 21, 1999. The issue of contamination of control animal plasma levels was discussed, and it was concluded that the low levels of contamination would not have altered the study outcome. Factors contributing to this conclusion were the small numbers of animals affected and lack of evidence for tumor findings in any group.

In the rat study, there were marked decreases in body weight among middle and high dose animals compared to controls. Since there were also some decreases in food intake in those groups, there was concern that palatability rather than drug toxicity may have been the cause. If that were the case, evidence that an MTD had been reached would be lacking because of the absence of dose-limiting toxicity. It was ultimately decided that palatability probably was not the cause of the decreased body weights, based on findings of decreased weight in the absence of a food effect in one month and 26-week rat dietary studies. The committee agreed that gavage would have been a more appropriate route of administration, and probably would have resulted in higher exposures. However, they considered the rat study to be an acceptable negative study, pending results of the ongoing European audits noted above, which have subsequently been received and indicate that the study was not compromised. It is theoretically possible that the results of the ongoing peer review of the rat study by the sponsor could have an impact on labeling, if it is determined that slides were read incorrectly and that there was an increase in some tumor type which we did not know about. This is quite unlikely, however.

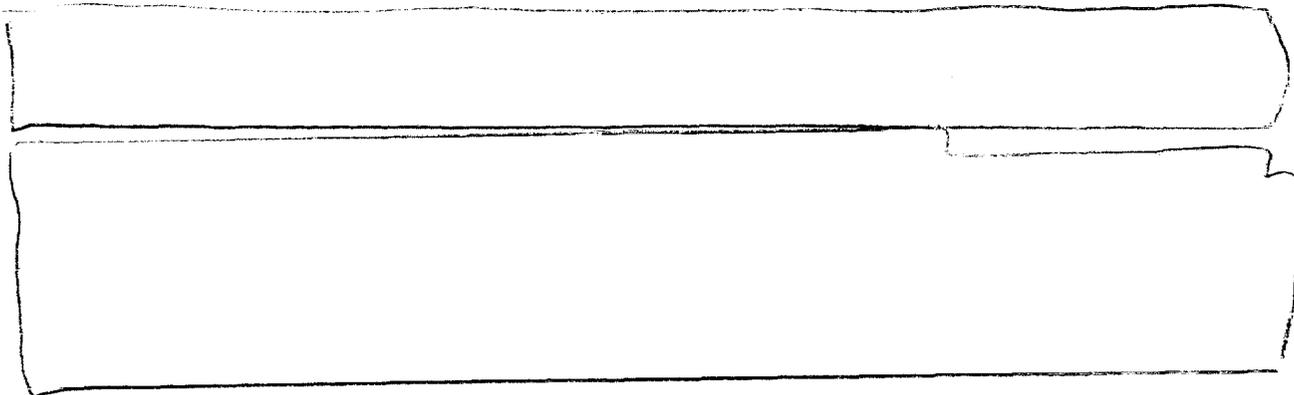
The committee recommended that the mouse study be considered unacceptable because no toxicity was observed and body weights were not significantly reduced, i.e., an MTD was not reached. In addition (although not reasons in and of themselves to consider the study unacceptable), the study was only 80 weeks in duration (rather than 104), and only low multiples of human exposures were achieved. Dr. Burris disagrees with the CAC and accepts the mouse study (see pages 16 - 18 of her review) and considers that the male cell was near an MTD based on weight effects. She does recommend a Phase 4 commitment to repeat the female mouse using higher doses. It is my recommendation that the entire mouse study be repeated in view of the fact that the original study was shorter than the current standard, toxicity was not demonstrated, and an effect on palatability was not ruled out as the cause of the body weight effects in males.

A gavage study would be more appropriate than a dietary one, since palatability may contribute to decreased weights in dosed mice. However, if the dietary route is to be used, the sponsor should conduct a 3-month study not only to determine doses for the definitive study but also to examine the possibility that there is a palatability effect in mice.

Levetiracetam was not mutagenic or clastogenic in a standard battery of assays. The major human metabolite (which is a hydrolysis product also present in animal species), was not mutagenic in two *in vitro* assays.

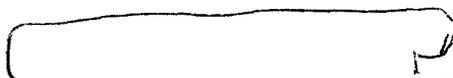
**Recommendations:**

This NDA is approvable for Pharmacology and Toxicology with the condition that the sponsor agrees to the following two commitments:



Recommended labeling is appended to this memo.

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 10/99  
Glenna G. Fitzgerald, Ph.D.  
Pharmacology Team Leader

NDA 21-035  
cc Division File  
Katz\Freiman\Malandrucco\Burriss\Fitzgerald

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ON ORIGINAL

3 pages  
redacted

DRAFT

LABELING