Constitution Application for a Patent

We, ROUSSEL-UCLAF, a French Body Corporate,

65604/80

of 35 Boulevard des Invalides, 75007 Paris, France,

hereby apply for the grant of a Patent

for an invention entitled

Antriarhythmic Medicaments with Prolonged Action of which the Active Principle is α-[2-bis (1-Methyl Ethyl) Amino] Ethyl α-Phenyl 2-Pyridine Acetamide or One of Its Salts, Their Preparation and the Compositions Containing Them,

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered 79-31443 for a patent or similar protection made in France on 21st December, 1979.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 19th day of December 1980.

ROUSSEL-UCLAF
By its Patent Attorneys: CALLINAN AND ASSOCIATES
ANTIARRHYTHMIC MEDICAMENTS WITH PROLONGED ACTION OF WHICH THE ACTIVE PRINCIPLE IS α-[2-[(1-METHYL ETHYL)AMINO]ETHYL] α-PHENYL 2-PYRIDINE ACETAMIDE OR ONE OF ITS SALTS, THEIR PREPARATION AND THE COMPOSITIONS CONTAINING THEM

I Hubert Fritel
of 35 Boulevard des Invalides
75007 Paris, France
do solemnly and sincerely declare as follows:

1. I am/we are the applicant(s) for the patent/patent-of-addition.

2. I am/we are authorised by the said company to make this declaration on its behalf.

3. I am/we are the actual inventor(s) of the invention and the facts upon which the said company is entitled to make the application are as follows:

   The said company would, if a patent were granted upon an application made by the inventors, be entitled to have the patent assigned to it.

JOHN ROBERT BLOOR, of 51 Sevenfields, Highworth, Swindon, Wiltshire, Great Britain;
GEORGE HAYES, of 55, Priory Green, Highworth, Swindon, Wiltshire, Great Britain; and
JACQUES SER, of 19, avenue Detouche, 93250 Willetois, France

are the actual inventor(s) of the invention and the facts upon which the said Company is entitled to make the application are as follows:

The said company would, if a patent were granted upon an application made by the inventors, be entitled to have the patent assigned to it.

SIGNED

HERE

Par proclamation: Hubert Fritel
The inert material is an essential aspect of the present invention because it allows for the adjustment of the quantity of the active principle passing into solution in the blood in such a way that the active principle will still be active but it will not be toxic.

CLAIM

1. An antiarrhythmic pharmaceutical composition for oral use having a prolonged action, containing:
   a) α-[2-[bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridine-acetamide or one of its addition salts with the pharmaceutically-acceptable mineral or organic acids,
   b) an ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms,
   c) a physiologically inert material of which the solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre, and, optionally,
   d) a binding agent and/or a lubricant.
ANTIIARRHYTHMIC MEDICATIONS WITH PROLONGED ACTION OF WHICH THE ACTIVE PRINCIPLE IS 
[2-[BIS (1-METHYL ETHYL)AMINO]ETHYL] a-
PHENYL 2-PYRIDINE ACETAMIDe OR ONE OF ITS 
SALTS, THEIR PREPARATION AND THE COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of performing it known to me—"
The present invention relates to antiarrhythmic medicaments with prolonged action whose active principle is α-[2-[bis(1-methyl ethyl)amino]ethyl]-α-phenyl 2-pyridine acetamide or one of its salts, their preparation and the compositions containing them.

It is known that the absorption of medicinal substances by the system is of very variable duration and amount according to the routes of administration. This absorption enables, in the most favourable cases, quick activity which can last for a few hours to be obtained.

In order to spread this activity over a period, various expedients are resorted to; from a physical point of view it is possible thus to modify the shape of the particles of active principle, to coat the latter or to incorporate it in an appropriate substance; in addition, chemical expedients have been contrived such as the use of ion exchange resins or complexing.
In the field of antiarrhythmics, it is more particularly useful to obtain products acting in a lasting manner and whose action is as constant as possible since the complaint to be treated requires most often uninterrupted therapy for a long period.

The Applicant has discovered a new delay form of a known antiarrhythmic medicament, namely -[2-bis (1-methyl ethyl)amino]ethyl]-α-phenyl-2-pyridine acetamide and its salts, such as the phosphate, the chloride, the bromide, the ethylene disulphonate, the acetate or the acid sulphate of sodium, described in Australian Patent No. 269,171 and United States Patent No. 3,225,054.

Thus the subject of the present invention is an antiarrhythmic pharmaceutical composition for oral use having a prolonged action, containing:

a) α-[2-[bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridine-acetamide or one of its addition salts with the pharmaceutically-acceptable mineral or organic acids,

b) an ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms,

c) an inert material of which the solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre, and optionally,

d) a binding agent and/or a lubricant.
The ester of glycerin and of a fatty acid can be a mono-, di-, or triester of glycerin, formed with fatty acids containing from 10 to 22 carbon atoms; there may be mentioned, for example, the mono-, di- and tristearates of glycerin, the mono-, di- and tripalmitates of glycerin, the di- and
trilaurates of glycerin, the mono-, di- and tricaprates of glycerin and the mono-, di- and trimyristates of glycerin. These esters can be used alone or in admixture.

Any material which has the required solubility and which is normally employed as an excipient in pharmaceutical formulations can be used as the inert material. The inert material is physiologically inert, without pharmacological properties.

The inert materials whose solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre can be, for example, mineral salts such as sodium chloride or sugars such as saccharose, lactose or glucose.

The inert material is an essential aspect of the present invention because it allows for the adjustment of the quantity of the active principle passing into solution in the blood in such a way that the active principle will still be active but it will not be toxic. This latter feature is an essential feature for a product used in cardiac treatment, which if used improperly, could prove to be fatal. In the absence of the inert material in the present invention, the active principle would be liberated very slowly and would be ineffective; in the presence of a more significant amount of inert material the active principle would be present in toxic concentrations and subsequently it would rapidly become inactive, because all the active principle would have
been liberated too rapidly. The retarding agent remains unaltered, in the form of a matrix, in the organism. The inert material and the active principle are soluble in the gastro-intestinal liquids and pass into solution in them. The matrix of the retarding agent releases the active principle all the more rapidly as it is mixed with the water soluble products.

Among the medicaments, which form the subject of the present invention, there are considered especially the medicaments containing α-[2-[bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridineacetamide phosphate.

Among the latter are considered the medicaments containing 60% to 80% of α-[2-[bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridine-acetamide, 10% to 30% of an ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms, and 2% to 12% of an inert material whose solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre.

Among the medicaments which form the subject of the present invention are considered particularly those wherein the ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms is glycercyl monostearate.

Also considered are those wherein the
inert material has a solubility in water at ambient temperature between 1.5 g and 2.5 g per millilitre and, among the latter, those characterized in that the inert vehicle is constituted by saccharose.

Within the scope of the present invention, it has also been found that it could be advantageous to add to the three components defined above a binding agent such as polyvinyl pyrrolidone and a lubricant.

Thus the subject of the present invention is also the medicaments as defined above, characterized in that they contain, in addition, polyvinyl pyrrolidone and a lubricant.

The lubricant can be, for example, talc, stearic acid, zinc, calcium or aluminium stearates and preferably magnesium stearate.

The binding agent and the lubricant can be added in the usual proportions, for example from 0.5% to 5% of each, and preferably from 0.5% to 1.5% of binding agent and from 2% to 3% of lubricant.

The medicaments as defined above are endowed with remarkable prolonged antiarrhythmic properties. These properties are illustrated further on in the experimental portion.

Because of these properties, the medicaments which form the subject of the present invention can be used in the preventive treatment of rhythm disorders, arrhythmism relapses, paroxysmal tachycardia relapses or in the curative treatment of auricular or ventricular extrasystole and digitalic
extrasystole and digitalic bigeminy.

The usual dose, which can be varied according to the product used, the subject treated and the complaint concerned can be, for example, from 100 mg to 500 mg of α-[2-[bis (1-methylethyl)amino]ethyl]-α-phenyl-2-pyridineacetamide phosphate per dose, by oral route in man, at the rate of one dose morning and evening.

Thus the subject of the invention is a process for preparing the medicaments as defined above, in that the different constituents, as defined above, are mixed according to techniques known per se.

Finally the subject of the invention is the pharmaceutical compositions which contain at least one medicament as described above, and a pharmaceutically acceptable excipient. These compositions are intended for the oral route.

These pharmaceutical compositions can be presented in the pharmaceutical forms currently used in human medicine for example, plain or sugar-coated compressed tablets, gelatin capsules and granules; they are prepared according to the usual methods.

When the pharmaceutical compositions as defined above are being made up other excipients usually used in these pharmaceutical compositions, such as gum arabic, aluminium hydroxide, colloidal silica, starch and preservatives, can be added. Such of these excipients as conform with the solubility requirements set out previously may be used as the said inert material.
There will now be given, not by way of limitation, an example of carrying out the invention.
EXAMPLE: Coated compressed tablets.

Coated compressed tablets were prepared, corresponding to the formula:

- \( \alpha-[2-\text{bis}(1\text{-methylethyl})\text{amino}.ethyl]-\alpha\text{-phenyl}-2\text{-pyridineacetamide phosphate} \) (disopyramide phosphate) \( \ldots \) 322.5 mg
- glycercyl monostearate \( \ldots \) 90.0 mg
- powdered sugar \( \ldots \) 30.0 mg
- polyvinyl pyrrolidone \( \ldots \) 5.0 mg
- magnesium stearate \( \ldots \) 12.5 mg
- coating (hydroxypropylmethyl cellulose, glucose, propyleneglycol) \( \ldots \) 10.0 mg

The \( \alpha-[2-\text{bis}(1\text{-methylethyl})\text{amino}.ethyl]-\alpha\text{-phenyl}-2\text{-pyridineacetamide phosphate} \), the glycercyl monostearate and the sugar are mixed homogeneously, the mixture is melted at about 65°C, the granules obtained are calibrated on a sieve, the said granules are moistened using an aqueous solution of polyvinyl pyrrolidone, dried and calibrated again, the magnesium stearate is added then the whole is passed into a tableting machine.

The coating is carried out by spraying with an aqueous solution of a mixture of hydroxypropylmethyl cellulose, glucose and propylene glycol and simultaneously drying.

Clinical study of the delayed activity.

The plasma concentrations of disopyramide are compared in man, as a function of time, after administration by oral route of 2 gelatin capsules containing 100 mg of disopyramide and one compressed tablet of disopyramide phosphate of the
Example, corresponding to 250 mg of disopyramide base.

The study dealt with 6 subjects of male sex, 21 to 24 years old, with overlapping administration.

The plasma samples (10 ml each time) were taken at times 0 (just before administration) - 0.5-1-1.5-2-3-4-5-6-8-12-15-24-30-36-48 hours after administration. The analysis of the product is carried out by high pressure liquid chromatography, after extraction of the plasma using ethyl acetate.

So as to be able to compare directly the plasma concentrations obtained after the administration, given that different doses of disopyramide are contained in the gelatin-capsules and in the compressed tablets, the concentrations were expressed in percentage of the dose administered per litre of plasma. The results obtained are as follows:

a) Timetables of maximum concentration:

The maximum plasma concentration is reached over 2.58 hours for the gelatin-capsule form and over 4.50 hours for the compressed-tablet form.

b) Amount of active principle attaining general circulation:

The area included between the curve representing the plasma concentration of the product tested as a function of the time and the axis of the abscissae is calculated. Substantially identical results are obtained.

Gelatin capsules : 13.6 % of the dose 1⁻¹ h
Compressed tablets: 13.2 % of the dose 1⁻¹ h

1 represents the plasma volume in litres
h represents the time in hours.
c) Latent period before the beginning of the action:
Gelatin capsules : 0.34 h
Compressed tablets : 0.29 h.

Conclusions:

A significant delay in the resorption of the product in the compressed-tablet form can thus be ascertained with reference to the gelatin-capsule form, given that the peak of maximum concentration is more retarded in the compressed-tablet form.

In addition, the same total quantity of active principle attains general circulation in the compressed-tablet and gelatin-capsule forms. Finally, the active principle appears in the plasma at identical times.

In the case of the compressed tablets, one is, therefore, dealing with medicaments with prolonged action.
The claims defining the invention are as follows:

1. An antiarrhythmic pharmaceutical composition for oral use having a prolonged action, containing:
   a) \( \alpha-[2-[\text{bis}(1\text{-methylethyl})\text{amino}]\text{ethyl}]\alpha\text{-phenyl-2-pyridine-acetamide} \) or one of its addition salts with the pharmaceutically-acceptable mineral or organic acids,
   b) an ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms,
   c) a physiologically inert material of which the solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre, and, optionally,
   d) a binding agent and/or a lubricant.

2. An antiarrhythmic pharmaceutical composition for oral use having a prolonged action, containing 60% to 80% of \( \alpha-[2-[\text{bis}(1\text{-methylethyl})\text{amino}]\text{ethyl}]\alpha\text{-phenyl-2-pyridine-acetamide} \), 10% to 30% of an ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms and 2% to 12% of an inert material whose solubility in water at ambient temperature is between 0.2 g and 3 g per millilitre.

3. A pharmaceutical composition as claimed in claim 2, wherein the ester of glycerin and of a fatty acid containing from 10 to 22 carbon atoms is glyceryl monostearate.

4. A pharmaceutical composition as claimed in any one of claims 1 to 3, wherein the said inert material has a solubility in water at ambient temperature between 1.5 g and 2.5 g per millilitre.
5. A pharmaceutical composition as claimed in claim 4, wherein the said inert material is constituted by saccharose.

6. A pharmaceutical composition as claimed in any one of claims 1 to 5, containing in addition, polyvinyl pyrrolidone and a lubricant.

7. Process for preparing a pharmaceutical composition as claimed in any one of claims 1 to 6, wherein the different constituents as defined in these claims are mixed according to techniques known per se.

8. A method of treatment of humans or warm-blooded animals for the prevention of rhythm disorders, arrhythmia relapses or paroxysmal relapses which comprises the administration of an effective amount of a pharmaceutical composition claimed in any one of claims 1 to 6.

9. A method of therapeutic treatment of a human or warm-blooded animal suffering from auricular or ventricular extrasystole, digitalic extrasystole or digitalic bigeminy, which comprises the administration of an effective amount of a pharmaceutical composition claimed in any one of claims 1 to 6.

10. A method of treatment as claimed in claim 8 or claim 9 wherein the dose of \( \alpha-[2-[\text{bis}(1\text{-methyl)ethyl}])\text{amino}]\text{ethyl} \)
- \( \alpha-[2-[\text{bis}(1\text{-methyl)ethyl}])\text{amino}]\alpha\text{-phenyl}-2\text{-pyridine-acetamide phosphate by oral route in man is from 100 mg to 500 mg,} \)
morning and evening.

DATED this 6th day of February, 1985.

ROUSSEL-UCLAF
By its Patent Attorneys:
CALLINAN AND ASSOCIATES