Abstract:

Use of dronedarone for the preparation of a medicament for use in the prevention of permanent atrial fibrillation
DRONEDARONE FOR THE PREVENTION OF PERMANENT ATRIAL FIBRILLATION

The instant invention relates to the use of dronedarone for the preparation of a medicament for use in the prevention of permanent atrial fibrillation.

2-n-butyl-3-[4-(3-di-n-butylaminopropoxy)benzoyl]-5-methylsulfonamido-benzofuranne or dronedarone and its pharmaceutically acceptable salts are described in European patent EP 0 471 609 B1.

Dronedarone is a multi-channel blocker that affects calcium, potassium and sodium channels and has anti-adrenergic properties.

Dronedarone is an anti-arrhythmic agent for the treatment of patients with a history of atrial fibrillation or atrial flutter.

Atrial fibrillation (AF) affects about 2.3 million people in North America and 4.5 million people in the European Union and is emerging as a growing public health concern because of the aging of the population.

AF is a condition in which the upper chambers of the heart beat in an uncoordinated and disorganized fashion, resulting in a very irregular and fast rhythm (i.e., an irregularly, irregular heartbeat). When blood is not completely pumped out of the heart's chambers, it can pool and clot. If a blood clot forms in the atria, exits the heart and blocks an artery in the brain, a stroke results. Consequently, about 15 percent of strokes result from AF.

AF is increasingly frequent with advancing age and is often caused by age-related changes in the heart, physical or psychological stress, agents that stimulate the heart, such as caffeine, or as a result of cardiovascular disease. The number is expected to double in the next 20 years. Without appropriate management, AF can lead to serious complications, such as stroke and congestive heart failure.

It is know that atrial fibrillation itself can cause changes in the electrical parameters of the heart known as electrical remodelling and in the structure of the cardiac chambers known as structural remodelling which tend to decrease the chances of the patient to get back into normal sinus rhythm. This vicious circle whereby "atrial fibrillation begets atrial fibrillation" has been well documented since the 1990s (Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A
It explains why when patients have been in atrial fibrillation for a long time they develop permanent atrial fibrillation with little or no chance to recover from this arrhythmia which becomes chronic.

The Inventors have now found that dronedarone reduces the likelihood of staying in / developing permanent AF and thus prevents patients from permanent atrial fibrillation/flutter.

The subject of the instant invention is the use of dronedarone or one of its pharmaceutically acceptable salts for the preparation of a medicament for use in the prevention of permanent atrial fibrillation/flutter in patients with a history of atrial fibrillation or atrial flutter.

More precisely, the invention relates to the use of dronedarone or one of its pharmaceutically acceptable salts for the preparation of a medicament for use in the prevention of about 33% of cardiovascular hospitalization or death of patients with permanent atrial fibrillation.

The percentage above corresponds to an average.

Among the pharmaceutically acceptable salts of dronedarone, mention may be made of the hydrochloride.

It will also be specified that the expression "having a history of atrial fibrillation or atrial flutter", "with a history of or a current atrial fibrillation or flutter" or "with a recent history of or a current atrial fibrillation or flutter" or "with paroxysmal or persistent atrial fibrillation or flutter" or "with a history of, or a current paroxysmal or persistent atrial fibrillation or flutter" or "with a recent history of, or a current paroxysmal or persistent atrial fibrillation or flutter" means a patient who, in the past, has presented one or more episodes of atrial fibrillation or flutter and/or who is suffering from atrial fibrillation or atrial flutter at the time the dronedarone or a pharmaceutically acceptable salt thereof is used. More particularly, this expression means patients with documentation of having been in both atrial fibrillation or flutter and sinus rhythm within the last 6 months preceding the start of treatment. Patients could be either in sinus rhythm, or in atrial
fibrillation or flutter at the time the dronedarone or a pharmaceutically acceptable salt thereof is initiated.

In the instant invention, "atrial fibrillation" means atrial fibrillation and/or atrial flutter.

Among the patients having a history of atrial fibrillation or atrial flutter, mention may also be made of patients also exhibiting at least one of the following risk factors:
- age notably equal to or above 70, or even above 75,
- hypertension,
- diabetes,
- history of cerebral stroke or of systemic embolism,
- left atrial diameter greater than or equal to 50 mm measured by echocardiography,
- left ventricular ejection fraction less than 40%, measured by two-dimensional echography.

Among patients with a history of atrial fibrillation or atrial flutter, mention may also be made of patients having additional risk factors corresponding to at least one of the following diseases:
- hypertension,
- structural heart disease,
- tachycardia,
- coronary heart disease,
- non-rheumatic valvular heart disease,
- ischemic dilated cardiomyopathy,
- a history of ablation for AF/AFL for example catheter ablation or surgical ablation,
- supra-ventricular tachycardia other than AF/AFL,
- history of cardiac valve surgery,
- non-ischemic dilated cardiomyopathy,
- hypertrophic cardiomyopathy,
- rheumatic valvular heart disease,
- sustained ventricular tachycardia,
- congenital heart disease,
- a history of ablation for other reason than AF/AFL for example catheter ablation,
- ventricular fibrillation,
and/or at least a cardiac device chosen among:
- a pacemaker,
- an implanted cardioverter defibrillator.

Cardiovascular hospitalizations means hospitalization having for main causes one of the following diseases: (Hohnloser and al., Journal of cardiovascular electrophysiology, janv 2008, vol. 19, n°1, pages 69-73):
- atherosclerosis related,
- myocardial infarction or unstable angina,
- stable angina pectoris or atypical chest pain,
- syncope,
- TIA or stroke (except intracranial haemorrhage),
- Atrial fibrillation and other supraventricular rhythm disorders,
- Non fatal cardiac arrest,
- Ventricular arrhythmia,
- Cardiovascular surgery except cardiac transplantation,
- cardiac transplantation,
- implantation of a pacemaker, of a implantable cardioverter defibrillator (« ICD ») or any other cardiac device,
- transfusaneous coronary, cerebrovascular or peripheral procedure,
- blood pressure related (hypotension, hypertension, except syncope),
- cardiovascular infection,
- major bleeding (requiring two or more units of blood or any intracranial haemorrhage),
- pulmonary embolism or deep vein thrombosis,
- worsening CHF including pulmonary edema or dyspnea of cardiac origin.

"Death" means death from any cause, cardiovascular or non cardiovascular.

Another object of the invention is a pharmaceutical composition which comprises, as active principle, dronedarone and pharmaceutically acceptable salts thereof according to the present invention. This pharmaceutical composition comprises...
an effective dose of at least dronedarone, or an addition salt thereof with a pharmaceutically acceptable salt, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable excipient. Said excipients are chosen according to the pharmaceutical form and the administration route desired, among usual excipients known to one of skill in the art.

In the pharmaceutical compositions according to the invention for the oral, sublingual, sub-cutaneous, intramuscular, intra-venous, topical, local, intratracheal, intranasal, transdermal or rectal administration, dronedarone or its salt, solvate or hydrate, can be administered as a unitary dosage form, in blend with usual pharmaceutical excipients, to animals and human beings for the prevention or for the treatment of pathological states mentioned above. The appropriate unitary dosage forms comprise the oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions or suspensions, the sublingual, buccal, intratracheal, intraocular, intranasal forms, the forms adapted to inhalation, topical, transdermal, sub-cutaneous, intramuscular or intra-venous delivery, the rectal forms and the implants. For the topical application, the compounds of the invention may be used as creams, gels, ointments or lotions.

For their therapeutic use, dronedarone and pharmaceutically acceptable salts thereof are generally introduced into pharmaceutical compositions.

These pharmaceutical compositions contain an effective dose of dronedarone or of a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

Said pharmaceutical composition may be given once or twice a day with food.

The dose of dronedarone administered per day, orally, may reach 800 mg, taken in one or more intakes, for example one or two.

More specifically, the dose of dronedarone administered may be taken with food.
More specifically, the dose of dronedarone administered per day, orally, may reach 800 mg, taken in two intakes with a meal.

The dose of dronedarone administered per day, orally may be taken at a rate of twice a day with a meal for example with the morning and the evening meal.

More specifically, the two intakes may comprise same quantity of dronedarone.

In the pharmaceutical compositions for the oral, sublingual, sub-cutaneous, intramuscular, intra-venous, topical, local, intratracheal, intranasal, transdermal or rectal administration, dronedarone or one of its pharmaceutically acceptable salts, can be administered as a unitary dosage form, in blend with usual pharmaceutical excipients, to animals and human in diseases above mentioned.

The appropriate unitary dosage forms comprise the oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions or suspensions, the sublingual, buccal, intratracheal, intraocular, intranasal forms, by inhalation, the topical, transdermal, sub-cutaneous, intramuscular or intra-venous forms, the rectal forms and the implants. For the topical application, the compounds of the invention may be used as creams, gels, ointments or lotions.

As an example, a unitary dosage form for dronedarone or one of its pharmaceutically acceptable salts, in the form of a tablet, can comprise the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg</th>
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<tbody>
<tr>
<td>dronedarone hydrochloride (corresponding to 400 mg of base)</td>
<td>426</td>
</tr>
<tr>
<td>Methylhydroxypropylcellulose</td>
<td>21.1</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>46.55</td>
</tr>
<tr>
<td>Modified corn starch</td>
<td>45.5</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>65</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>40</td>
</tr>
<tr>
<td>Anhydrous colloidal silica</td>
<td>2.6</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>3.25</td>
</tr>
<tr>
<td></td>
<td>650</td>
</tr>
</tbody>
</table>
For oral administration, dronedarone daily dose may reach 800 mg.

In specific cases, higher or lower dosages may be appropriate; these dosages are comprised within the scope of the present invention. According to usual practice, the dosage suitable to each patient is determined by the physician according to the administration route, the weight, the disease, the body surface, the cardiac output and response of the patient.
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The instant invention also relates to a method of treatment of the above mentioned disease which comprises the administration to a patient of an effective dose of at least dronedarone or one of its pharmaceutically acceptable salts.

5 The invention is illustrated with the data below.

Efficacy of dronedarone and its pharmaceutically acceptable salts versus placebo for the prevention of permanent atrial fibrillation was provided via dronedarone hydrochloride during a prospective, multinational, double-blind, randomized, multi-center, placebo-controlled, parallel group trial.

1. Selection of patients

Patients must have a history of atrial fibrillation or atrial flutter and/or may be in normal sinus rhythm or in atrial fibrillation or flutter at the time of recruitment.

Recruitment of patients was conducted taking into account the following inclusion criteria:

20 Inclusion criteria:

1) One of the following risk factors had to be present:

- age equal to or greater than 70 years,
- hypertension (taking antihypertensives of at least two different classes),
- diabetes,
- history of cerebral stroke (transient ischemic event or completed cerebral stroke) or of systemic embolism,
- left atrial diameter greater than or equal to 50 mm measured by echocardiography,
- left ventricular ejection fraction less than 40%, measured by two-dimensional echography;

or
- age equal to or above 70, or even above 75, possibly combined with at least one of the risk factors below:
  - hypertension (taking antihypertensives of at least two different classes),
  - diabetes,
  - history of cerebral stroke (transient ischemic event or completed cerebral stroke) or of systemic embolism,
  - left atrial diameter greater than or equal to 50 mm measured by echocardiography,
  - left ventricular ejection fraction less than 40%, measured by two-dimensional echography;

2) availability of one electrocardiogram within the last six months, showing that the patient was or is in atrial fibrillation/flutter,

3) availability of one electrocardiogram within the last six months, showing that the patient was or is in sinus rhythm.

II. Duration and treatment

Study drug treatment units (placebo or dronedarone hydrochloride corresponding to 400 mg of base) were such that each patient took one tablet in the morning during or shortly after breakfast and one tablet in the evening during or shortly after dinner.

The treatment duration depended on the time of recruitment of each patient in the trial and could be comprised from 12 months to 30 months.

III. Results

From the 4628 patients included in the trial, 2301 were part of the group treated with dronedarone hydrochloride.

"Patients with permanent atrial fibrillation or flutter" means patients with a history of atrial fibrillation or atrial flutter, who were in atrial fibrillation or flutter at the time of
recruitment but who had not a previous history of permanent atrial fibrillation or flutter and who stayed in permanent atrial fibrillation or flutter during all the trial.

Results relating to the prevention of permanent atrial fibrillation/flutter

The number of patients with permanent atrial fibrillation/flutter was compared using Fischer's exact test. 294 patients had permanent atrial fibrillation/flutter in the group treated with placebo versus 178 patients in the group treated with dronedarone hydrochloride (p<0.001). It indicates a decrease of the likelihood of developing permanent AF. Consequently, dronedarone prevents the risk of permanent atrial fibrillation/flutter.

Results relating to the prevention of cardiovascular hospitalization or death

The results obtained during this trial were analyzed by the Kaplan Meier method for the figures and the relative risk (RR) was estimated using Cox's proportional effect regression model.

The relative risk (RR) is the ratio of the rates of occurrence of a hospitalization or death in patients receiving dronedarone compared with patients receiving a placebo.

The percentage reduction x of a given event (hospitalization, death, cardiovascular death and the like) is calculated in the following manner:

\[ x = 1 - \text{relative risk}. \]

Of the 4628 patients included in the study, 2301 formed part of the group treated with dronedarone hydrochloride. 294 patients were in permanent atrial fibrillation in the placebo group against 178 in the group treated with dronedarone hydrochloride.

74 events were recorded in the placebo group against 29 in the group treated with dronedarone hydrochloride. The calculated relative risk is 0.67 with p = 0.06, that is a 33% reduction in cardiovascular hospitalizations and deaths under dronedarone hydrochloride.
CLAIMS


2. Use according to claim 1, characterized in that the patients have a history of atrial fibrillation or atrial flutter.

3. Use according to claims 1 or 2, characterized in that the patients have at least one of the following risk factors:
   - age notably equal to or above 70, or even above 75
   - hypertension,
   - diabetes,
   - prior cerebrovascular accident or systemic embolism,
   - left atrium diameter greater that or equal to 50 mm by echocardiography,
   - left ventricular ejection fraction less than 40% by 2D-echocardiography.

4. Use according to claims 1, 2 or 3, characterized in that the patients have additional risk factors corresponding to at least one of the following diseases:
   - hypertension,
   - structural heart disease,
   - tachycardia,
   - coronary heart disease,
   - non-rheumatic valvular heart disease,
   - ischemic dilated cardiomyopathy,
   - ablation for AF/AFL,
   - supra-ventricular tachycardia other than AF/AFL,
   - history of cardiac valve surgery,
   - non-ischemic dilated cardiomyopathy,
   - hypertrophic cardiomyopathy,
   - rheumatic valvular heart disease,
   - sustained ventricular tachycardia,
   - congenital heart disease,
   - ablation for other reason than AF/AFL,
   - ventricular fibrillation,
and/or at least a cardiac device chosen among:
- a pacemaker,
- an implanted cardioverter defibrillator.

5. Use according to one of the preceding claims, characterized in that, for oral administration, dronedarone daily dose may reach 800 mg.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/343 A61P9/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Relevant to claim No</th>
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<tr>
<td>A</td>
<td>&quot;Continuous Versus Episodic Amiodarone Treatment for the Prevention of Permanent Atrial Fibrillation&quot;</td>
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<td></td>
<td>ISSN: 0195-668X</td>
<td>the whole document</td>
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X Further documents are listed in the continuation of Box C
D See patent family annex

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance
'B' earlier document but published on or after the international filing date
'L' document which may throw doubts on novelty claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'S' document published prior to the international filing date but later than the priority date claimed
'I' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
'S' document member of the same patent family

Date of the actual completion of the international search
3 November 2009

Date of mailing of the international search report
17/11/2009

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Authorized officer
Scheithe, Rupert
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<td>A</td>
<td>&quot;THE MERCK MANUAL OF DIAGNOSIS AND THERAPY EIGHTEENTH EDITION&quot; 2006, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION, NJ, XP002553410 pages 697-699 especially page 697, left hand column, chapter &quot;Etiology and Classification&quot;</td>
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