(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030207 A1

(51) International Patent Classification[7]: A61K 31/439, 31/4995, A61P 9/00, 9/06

(21) International Application Number:
PCT/EP2004/052310

(22) International Filing Date:
24 September 2004 (24.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/505,763	26 September 2003 (26.09.2003)	US
03103574.4	26 September 2003 (26.09.2003)	EP

(71) Applicant: **SOLVAY PHARMACEUTICALS GMBH** [DE/DE]; Hans-Böckler-Allee 20, 30173 Hannover (DE).

(72) Inventors: **THORMAEHLEN, Dirk**; c/o Solvay Pharmaceuticals GmbH, Hans-Boeckler-Allee 20, 30173 Hannover (DE). **STRAUB, Matthias**; c/o Solvay Pharmaceuticals GmbH, Hans-Boeckler-Allee 20, 30173 Hannover (DE). **JANSEN, Jan**; c/o Solvay Deutschland GmbH, Hans-Boeckler-Allee 20, 30173 Hannover (DE). **ANTZELEVITCH, Charles**; c/o Solvay Pharmaceuticals GmbH, Hans-Boeckler-Allee 20, HANNOVER 30173 (DE).

(74) Agent: **GOSMANN, Martin**; c/o Solvay Pharmaceuticals GmbH, Intellectual Property & Scientific Information, Hans-Böckler-Allee 20, 30173 Hannover (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF 3, 7-DIAZABICYCLO (3.3.1) NONANE COMPOUNDS FOR THE TREATMENT OF BRUGADA SYNDROME

(57) Abstract: The present invention relates to the use of 3,7-diazabicyclo[3,3, 1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3, 1]nonane compounds, and most preferably to the use of tedisamil, and the physiologically acceptable acid addition salts and/or solvates thereof, for the treatment and/or prophylaxis of the Brugada syndrome and/or symptoms.

WO 2005/030207 A1

USE OF 3,7-DIAZABICYCLO(3.3.1)NONANE COMPOUNDS FOR THE TREATMENT OF BRUGADA SYNDROME

Description

The present invention relates to a novel medicinal use of 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably to a novel medicinal use of tedisamil, and of pharmaceutically acceptable acid addition salts and/or solvates of said compounds.

9,9-Alkylene-3,7-diazabicyclononane compounds of formula I and their pharmacological activities are known from published European Patent No. EP 103,833 and the corresponding U.S. Pat. No. 4,550,112, and Finnish Patent No. FI 76,338. Compounds of formula I are a sub-group of the 9,9-N,N'-tetra-substituted 3,7-diaza-bicyclo[3.3.1]nonane compounds described in the aforementioned patent specifications and can be prepared by the methods described therein. The aforementioned patent specifications disclose that the compounds have useful cardio-active properties, particularly oxygen-saving effects and effects on the heart rate and heart rhythm in general, and are distinguished by a high physiological tolerance. Thus, the compounds show a satisfactory anti-arrhythmic action even at low doses. Moreover, the undesired negative effect on the contractile power of the heart is extremely low; i.e. the compounds have a particularly favourable ratio of anti-arrhythmic or the refractory period of the heart prolonging activities, to negative inotropic secondary activities.

Moreover, it is described in Burow et al., U.S. Pat. No. 5,164,401, the compounds also have a pronounced diuretic effect with a favourable ratio between sodium and potassium excretion.

Furthermore special salts and their manufacture of the 3,7-diazabicyclo[3,3,1]-nonane compounds, in particular of 9,9-alkylene-3,7-diazabicyclo[3,3,1]nonane compounds are described in US 5,324,732. Thus, US 5,324,732 describes fumaric acid salts of said compounds containing 1.5 moles of fumaric acid per mole of the compound.

It is the object of the invention to provide a novel medical use or a new method of treating patients in need of treatment and/or prophylaxis of the Brugada syndrome. Another object of the invention is to provide new pharmaceutical compositions suitable for the treatment and/or prophylaxis of the Brugada syndrome.

The objects of the invention are achieved by surprisingly discovering that 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably tedisamil, and of pharmaceutically acceptable acid addition salts and/or solvates of said compounds are particularly suitable for the treatment and/or prophylaxis of the Brugada syndrome. According to a further aspect of the invention, the objects are achieved by providing a pharmaceutical composition comprising an effective amount of at least one 3,7-diaza-bicyclo[3,3,1]nonane compound as described in the present invention, which are suitable for the treatment and/or prophylaxis of the Brugada syndrome.

Brugada syndrome (Mattu A; Rogers RL; Kim H; Perron AD; Brady WJ, "The Brugada syndrome", The American journal of emergency medicine; VOL: 21 (2); p. 146-51 /200303) describes the syndrome of sudden cardiac death in the setting of the following electrocardiographic findings: right bundle branch block pattern with ST-segment elevation in the right precordial leads. The right bundle branch block may be incomplete while the ST segment elevation is minimal. The electrocardiographic findings are not constant. In other words, the Brugada syndrome describes a group of patients at risk for the occurrence of ventricular fibrillation who have no definable structural heart disease associated with the right bundle branch block conduction pattern and ST-segment elevation in the right precordial leads. Patients suspected of having Brugada syndrome should be promptly referred for electrophysiological testing and appropriate treatment and/or prophylaxis. Thus, in the state of the art rapid referral of the patients and placement of an implantable cardioverter defibrillator (ICD) is associated with an excellent prognosis, whereas failure to diagnose this condition is associated with a high risk for sudden death. Because of the poor prognosis of Brugada patients (with up to a 10 % per year mortality), symptomatic patients are recommended in the state of the art to prophylactic implantation of an implantable cardioverter defibrillator to prevent sudden cardiac death.

Early diagnosis of conditions associated with Brugada or of the susceptibility to Brugada is essential to minimize the high risk for sudden death or life-threatening

ventricular arrhythmias. The Brugada syndrome is an arrhythmic syndrome which can be characterized as a primary electrical disease of the heart that causes sudden cardiac death, in particular secondary to ventricular tachyarrhythmias, or life-threatening ventricular arrhythmias, especially in younger men. Genetic analysis supports that this syndrome is a cardiac ion channel disease (defects in the alpha subunit of the sodium channel). This defect causes a reduction in the sodium channel current, which attenuates the epicardial action potential notch leading to ST-segment elevation. Consequently, as stated above a typical electrocardiographic finding consists of a right bundle branch block pattern and ST-segment elevation in the right precordial leads. The higher intercostal space V(1) to V(3) lead electrocardiogram and are discussed in the literature to potentially be helpful in detecting Brugada patients (Ikeda T, "Brugada syndrome: current clinical aspects and risk stratification.", Annals of noninvasive electrocardiology: the official journal of the International Society for Holter and Non-invasive Electrocardiology, Inc; VOL: 7 (3); p. 251-62 /200207). Although two types of the ST-segment elevation are present, the coved type is more relevant to the Brugada syndrome than the saddle-back type. These patterns can be present permanently or intermittently. The scientific literature also suggests that the Brugada-type electrocardiogram is more prevalent than the manifest Brugada syndrome. Asymptomatic individuals have a much lower incidence of future cardiac events than the symptomatic patients. Although risk stratification for the Brugada syndrome is still incomplete in the state of the art, the inducibility of sustained ventricular arrhythmias has been proposed as a good outcome predictor in this syndrome. In noninvasive techniques, some clinical evidence supports that late potentials detected by signal-averaged electrocardiography are a useful index for identifying patients at risk of Brugada syndrome.

It is also known from the state of the art that usually antiarrhythmic drugs, including beta-blockers and amiodarone have no beneficial effects in prolonging survival (Naccarelli GV; Antzelevitch C; "The Brugada syndrome: clinical, genetic, cellular, and molecular abnormalities.", The American journal of medicine; VOL: 110 (7); p. 573-81 /200105). In view of the ionic basis and arrhythmia mechanisms underlying the Brugada syndrome (Antzelevitch C; "The Brugada syndrome: Ionic Basis and Arrhythmia Mechanisms", Journal of Cardiovascular Electrophysiology, Vol. 12, No.2, Feb. 2001, 268-272), up to date, the treatment of choice is still the insertion of an implantable cardioverter-defibrillator (ICD). An state-of-the-art paper (Antzelevitch C; "The Brugada syndrome: 1992-2002, A Historical Perspective", Journal of the American College of Cardiology, Vol. 41, No. 10, 2003, 1665-71) gives a historical perspective on the

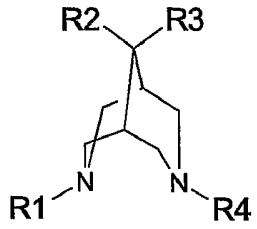
Brugada syndrome, an intriguing new clinical entity characterized by ST-segment evaluation in the right precordial electrocardiographic leads and a high incidence of sudden death in individuals with structurally normal hearts, which was first described by Pedro and Josep Brugada in 1992. Although great progress has been achieved in the characterization of the Brugada syndrome over the past decade, relatively little progress has been made in the approach to therapy. Implantation of an ICD is the only established effective treatment for this life-threatening disease. The need for cost-effective treatment or preventive measures is evident.

Therefore, it is not only imperative that all emergency physicians are familiar with the typical ECG manifestations of Brugada syndrome and the diagnosis thereof, but it is also rather essential that also beneficial methods of drug treatment and/or prophylaxis are available in order to reduce the high risk of sudden cardiac death and/or life-threatening ventricular arrhythmias in patients being susceptible to or with high risk at the Brugada syndrome or being symptomatic.

Hence, it is clear that there is a high unmet medical need to reduce the high risks caused by the Brugada syndrome, e.g. in particular to reduce the high risk of sudden cardiac death and/or life-threatening ventricular arrhythmias in Brugada patients or symptomatic patients, by suitable medication with drugs, either as sole preventive treating or in addition, e.g. as adjuvant treatment to ICD placement, and even before and still after ICD placement.

The subject of the invention is therefore directed to the use of the use of 3,7-diaza-bicyclo[3,3,1]nonane compounds, its physiologically acceptable acid addition salts and/or solvates thereof for the production of a pharmaceutical preparation for the treatment and/or prophylaxis of the Brugada syndrome and/or patients being symptomatic. The findings of the present invention generally apply equally to both genders, e.g. male and female patients, at any age. However, usually males are susceptible to a higher degree than females to the Brugada syndrome or to the symptomatic conditions, e.g. life-threatening ventricular arrhythmias, especially in younger men. Hence, about 90 % of the patients are male and only about 10 % are female. Furthermore, the invention is particularly suitable also for infants and young children or for adults residing in regions of the world where an ICD is unaffordable.

The compounds suitable for this novel medicinal use are 3,7-diazabicyclo[3,3,1]nonane compounds corresponding to the Formula I:



I

wherein

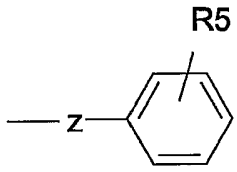
R1 represents an alkyl group containing from 1 to 6 carbon atoms, an alkylene group containing from 3 to 6 carbon atoms having a double bond which is not linked directly to the nitrogen atom, a cycloalkylalkyl group containing from 4 to 9 carbon atoms, or a benzyl group,

R2 represents a lower alkyl group, and

R3 represents a lower alkyl group, or

R2 and R3 together form an alkylene chain containing from 3 to 6 carbon atoms, and

R4 represents an alkyl group containing from 1 to 6 carbon atoms, an alkenyl group containing from 3 to 6 carbon atoms having a double bond which is not linked directly to the nitrogen atom, a cycloalkylalkyl group containing from 4 to 9 carbon atoms, a group corresponding to the Formula a:



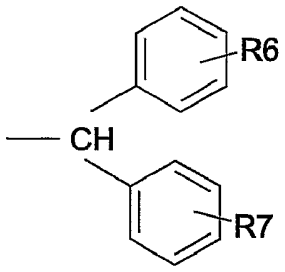
a

wherein

R5 represents hydrogen, halogen, lower alkyl or lower alkoxy, and

Z represents an alkylene chain containing from 1 to 3 carbon atoms or a propenylene chain having a double bond which is conjugated with the phenyl group, or

a group corresponding to the Formula b:



b

wherein

R6 represents hydrogen, halogen, lower alkyl or lower alkoxy, and

R7 represents hydrogen, halogen, lower alkyl or lower alkoxy,

or a physiologically acceptable acid addition salt and/or solvate thereof.

Particularly suited compounds for the novel medicinal use according to the invention are compounds of Formula I, wherein R1 represents an alkyl group containing from 1 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms. In further preferred compounds of Formula I the substituent R4 represents an alkyl group containing from 1 to 6 carbon atoms, a cycloalkylalkyl group containing from 4 to 7 carbon atoms, or a group corresponding to Formula b.

Preferred compounds for the novel medicinal use according to the invention are compounds of Formula I, wherein R1 represents an alkyl group containing from 3 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms, and R4 represents an alkyl group containing from 3 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms. Said 3,7-diazabicyclo-[3,3,1]nonane compound may be a 9,9-alkylene-3,7-diazabicyclo[3.3.1]nonane compound of Formula I wherein R2 and R3 together form an alkylene chain containing from 4 to 5 carbon atoms, and R1 and R4 independently of one another each denote a straight-chain or branched alkyl group of 3-4 carbon atoms or the cyclopropylmethyl group, and physiologically acceptable acid addition salts and/or solvates thereof. Preferred salts for this group of compounds are fumaric acid salts of 9,9-alkylene-3,7-diazabicyclo[3.3.1]nonane compounds containing 1.5 moles of fumaric acid per mole of compound of formula I.

Further preferred compounds for the novel medicinal use according to the invention are compounds selected from the group consisting of N,N'-dicyclopropyl-methyl-9, 9-tetramethylen-3,7-diazabicyclo[3,3,1]nonane (tedisamil), N-isobutyl-N'-isopropyl-9,9-pentamethylen-3,7-diazabicyclo[3,3,1]nonane, and physiologically

acceptable acid addition salts and/or solvates thereof. Preferred salts for this group of compounds are fumaric acid salts of N,N'-dicyclopropylmethyl-9, 9-tetramethylene-3,7-diazabicyclo[3,3,1]nonane (tedisamil) or of N-isobutyl-N'-isopropyl-9,9-pentamethylene-3,7-diazabicyclo[3,3,1]nonane containing 1.5 moles of fumaric acid per mole of said 9,9-alkylene-3,7-diazabicyclo[3.3.1]-nonane compound.

Alternatively, as acid addition salts of the 3,7-diazabicyclo[3,3,1]nonane compounds the hydrochloride salts are also very suitable for the novel medicinal use according to the present invention.

Particularly preferred 3,7-diazabicyclo[3,3,1]nonane compounds are the 9,9-alkylene-3,7-diazabicyclo[3.3.1]nonane compound tedisamil and the physiologically compatible acid addition salts and/or solvates thereof, these are most preferably used as compounds for the production of pharmaceutical preparations for the treatment and/or prophylaxis of of antiarrhythmic male patients, preferably in conversion of recent onset of atrial fibrillation (Afib) or flutter to normal sinus rhythm (NSR) in male patients. If a tedisamil acid addition salt is used, it may preferably be used according to the invention in the form of tedisamil hydrochloride or in the form of tedisamil sesquifumarate. Further pharmacologic-ally compatible acid addition salts of tedisamil are known from European Patent No. EP 103,833. Thus, salts with inorganic acids, e.g. sulfuric acid or hydrohalic acids, especially hydrochloric acid; or with organic acids, for instance lower aliphatic monocarboxylic or dicarboxylic acids such as acetic acid, fumaric acid, tartaric acid, lactic acid, maleic acid, citric acid or salicylic acid; or with sulfonic acids, for instance lower alkyl sulfonic acids such as methane sulfonic acid, or benzene sulfonic acids optionally substituted in the benzene ring by halogen or lower alkyl, such as p-toluene sulfonic acid, are suitable as physiologically acceptable acid addition salts of the compounds of Formula I.

Surprisingly, it has been found that the 3,7,9, 9-tetra-substituted 3,7-diazabicyclo[3,3,1]nonane compounds corresponding to Formula I are distinguished by superior effects in patients being subject to the Brugada syndrome or being diagnosed to be symptomatic, in addition to the aforementioned already known general heart-affecting properties. The superior effects of the compounds of Formula I in Brugada syndrome patients can be demonstrated by data derived from an experimental Brugada syndrome model, which data prove the surprising suitability of 3,7-diazabicyclo[3,3,1]nonane

compounds, e.g. of tedisamil and its acid addition salts, for the treatment and/or prophylaxis of the Brugada syndrome.

EXPERIMENTAL BRUGADA SYNDROME MODEL AND TEST RESULTS

The following experimental model shows that Tedisamil and comparable compounds, e.g. 3,7,9, 9-tetra-substituted 3,7-diazabicyclo[3,3,1]nonane compounds corresponding to Formula I, abolishe the arrhythmogenic substrate responsible for VT/VF in the Brugada Syndrome (VT = ventricular tachycardia; VF = ventricular fibrillation).

The Brugada syndrome (BS) is characterized by ST segment elevation in V1-V3 and the appearance of closely coupled extrasystoles capable of triggering polymorphic VT/VF. Previous studies from our laboratory have shown that a prominent transient outward current (I_{to})-mediated action potential (AP) notch in the right ventricular (RV) epicaridium (Epi) contributes to the electrocardiographic (ECG) characteristics of the syndrome. In the presence of a prominent I_{to}, I_{Na} inhibition can result in all-or-none repolarization at the end phase 1 of the AP at some Epi sites but not others, leading to phase 2 reentry and VT/VF. I_{to} block normalizes ST segment elevation and abolishes VT/VF. Tedisamil, an agent in clinical trials for atrial fibrillation indications, blocks I_{to} at clinically relevant concentrations. The actions of tedisamil in an arterially-perfused canine RV wedge model of the Brugada syndrome were evaluated.

Results: Terfenadine (5-7 μM) was used to create the BS phenotype. Floating microelectrode AP recordings were simultaneously obtained from epicardial and endocardial sites together with an ECG. At a basic cycle length (BCL) of 2000 msec, terfenadine accentuated Epi AP notch and ECG J wave, reducing Epi phase 1 amplitude from 66.1±3.9% to 55.1±2.4% of phase 2 amplitude (n=6, $p<0.05$). All-or-none repolarization was observed at some Epi sites but not others, leading to ST segment elevation in the ECG and development of phase 2 reentry. The closely coupled extrasystoles thus generated precipitated polymorphic VT/VF. Addition of tedisamil (2 μM) to the coronary perfusate restored the Epi AP dome, thus diminishing transmural and epicardial dispersion of repolarization. Phase 1 amplitude in Epi increased to 64.2±1.2% of phase 2 (n=6, $p<0.05$ vs. terfenadine alone). Tedisamil abolished phase 2

reentry-induced extrasystoles in 6/6 preparations, and polymorphic VT/VF in 3/3 preparations.

Conclusions: Tedisamil is effective in abolishing the arrhythmogenic substrate responsible for VT/VF in an experimental model of the Brugada syndrome and may be useful as an adjunct or alternative to ICD therapy in the clinic.

What is particularly surprising is the effectiveness of 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably of tedisamil, and of pharmaceutically acceptable acid addition salts and/or solvates in the treatment of patients showing the Brugada syndrome or being diagnosed to be symptomatic. This efficacy has never been observed before in a vast variety of investigations with tedisamil in many patients. This result is even more surprising as up to date there is no drug medication available to effectively prevent the risks associated with the Brugada syndrome, e.g. such as high risk of sudden cardiac death and/or life-threatening ventricular arrhythmias in Brugada patients or symptomatic patients. Nowhere, the present invention for the first time provides a promising and beneficial drug medication for the treatment and/or prophylaxis of the Brugada syndrome, substantially improving the prognosis of Brugada patients or symptomatic patients. The drug medication according to the present invention may by applied either as sole preventive treating, e.g. where no ICD placement is available at all or right away, or in addition to ICD placement, and even before and cotreatment still after ICD placement.

Finally, from the results regarding efficacy of tedisamil found in the experiments it may be summarized that tedisamil-like 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably tedisamil itself, as well as the acid addition salts, are particularly suited for the treatment and/or prophylaxis of the Brugada syndrome or symptomatic patients.

The invention therefore also pertains to a method of treatment and/or prophylaxis of the Brugada syndrome and/or Brugada-related symptoms characterized in that a 3,7-diazabicyclo[3,3,1]nonane compound corresponding to the Formula I (as defined above) is administered to a patient in need of such treatment and/or prophylaxis in an amount being effective to relieve, ameliorate and/or prevent said syndrome and/or symptoms, and in particular to minimize and/or prevent the risk of sudden cardiac death and/or life-

threatening ventricular arrhythmias. The treatment and/or prophylaxis according to the present invention generally apply equally to both genders, e.g. male and female patients, at any age. However, usually males are susceptible to a higher degree than females to the Brugada syndrome or to the symptomatic conditions, e.g. life-threatening ventricular arrhythmias, especially in younger men. Thus, in another aspect of the present invention the method of treatment and/or prophylaxis is characterized in that the Brugada syndrome and/or Brugada-symptomatic patients are male. In yet a further aspect of the present invention the method of treatment and/or prophylaxis is characterized in that the Brugada syndrome and/or Brugada-symptomatic patients are younger men, and then preferably the treatment and/or prophylaxis is directed to relieve, ameliorate and/or prevent life-threatening ventricular arrhythmias in said patients. The invention also pertains to a method of treatment and/or prophylaxis which is characterized in that the patients in need are infants and/or young children. In still further aspects of the invention the method of treatment and/or prophylaxis of the Brugada syndrome and/or Brugada-related symptoms is characterized in that the 3,7-diazabicyclo[3,3,1]nonane compound corresponding to the Formula I (as defined above) is administered either as sole preventive medical drug treating, e.g. where no ICD placement is available at all or right away, or in addition, e.g. as adjuvant treatment to ICD placement, in particular before and/or still after ICD placement.

As a therapeutic agent, 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably of tedisamil, and of pharmaceutically acceptable acid addition salts and/or solvates, may be contained according to the invention, together with conventional pharmaceutical auxiliaries and/or carriers, in solid or liquid pharmaceutical preparations. Examples of solid preparations are preparations which can be administered orally, such as tablets, coated tablets, capsules, powders or granules, or alternatively suppositories. These preparations may contain conventional pharmaceutical inorganic and/or organic carriers, such as talcum, lactose or starch, in addition to conventional pharmaceutical auxiliaries, for example lubricants or tablet disintegrating agents. Liquid preparations such as suspensions or emulsions of 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably of tedisamil, and of pharmaceutically acceptable acid addition salts and/or solvates thereof, may contain the usual diluents such as water, oils and/or suspension agents such as polyethylene glycols and the like. Other auxiliaries may additionally be added, such as preservatives, taste correctives and the like.

The 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably tedisamil, and pharmaceutically acceptable acid addition salts and/or solvates thereof, can be mixed and formulated with the pharmaceutical auxiliaries and/or carriers in known manner. For the production of solid medicament forms, 3,7-diazabicyclo-[3,3,1]nonane compounds, preferably of 9,9-alkylene-3,7-diazabicyclo[3,3,1]-nonane compounds, and most preferably tedisamil, and pharmaceutically acceptable acid addition salts and/or solvates thereof, can for example be mixed with the auxiliaries and/or carriers in conventional manner and can be wet or dry granulated. The granules or powder can be poured directly into capsules or be pressed into tablet cores in conventional manner. These can be coated in known manner if desired.

EXAMPLES

The following Examples 1 to 3 describe pharmaceutical preparations according to the invention which contain an active substance of Formula I, and also the production of such pharmaceutical preparations. The following examples explain the production of pharmaceutical preparations containing tedisamil dihydrochloride. Pharmaceutical preparations containing tedisamil sesquifumarate may be obtained in an analogous manner.

Example 1: Tablets Composition:

20 parts	of N,N'-dicyclopropylmethyl-9,9-tetramethylen-3,7-diazabicyclo[3,3,1]-nonane dihydrochloride
30 parts	of corn starch
55 parts	of lactose
5 parts	of polyvinylpyrrolidone
2 parts	of magnesium stearate
3 parts	of talcum

Total 115 parts

PREPARATION METHOD

The active substance was mixed with corn starch and finely powdered lactose in a mixer. The resulting mixture was thoroughly moistened with a 20% solution of polyvinylpyrrolidone ("Kollidon 25", from BASF) in deionized water. If necessary, additional deionized water was added. The moist granules were passed through a 2 mm sieve, dried on trays at 40 DEG C. and then passed through a 1 mm sieve (Frewitt machine). After the granules had been mixed with magnesium stearate and talcum, tablets weighing 115 mg were pressed therefrom, so that each tablet contained 20 mg of the active substance.

Example 2: Capsules Composition

20 parts	of N-isobutyl-N'-isopropyl-9,9-pentamethylen-3,7-diazabicyclo[3,3,1]nonane dihydrogen fumarate
20 parts	of corn starch
45 parts	of lactose
3 parts	of polyvinylpyrrolidone
1.5 parts	of magnesium stearate
0.5 parts	of highly dispersed silicic acid

Total 90 parts

PREPARATION METHOD

The active substance was mixed with corn starch and finely powdered lactose in a mixer. The resulting mixture was thoroughly moistened with a 20% solution of polyvinylpyrrolidone ("Kollidon 25", from BASF) in deionized water. If necessary, deionized water was added. The moist granules were passed through a 1.6 mm sieve (Frewitt machine), dried on trays at 40 DEG C., and then passed through a 1 mm sieve (Frewitt). After the granules had been mixed with magnesium stearate and highly dispersed silicic acid ("Aerosil 200", from Degussa), 90 mg thereof in each case were filled by means of an automatic encapsulating machine into size 4 hard gelatin capsules, so that each capsule contained 20 mg of active substance.

Example 3: Ampoules Composition (per ampoule)

5 mg	N,N'-dicyclopropylmethyl-9,9-tetramethylen-3,7-diazabicyclo[3,3,1]nonane dihydrochloride
16 mg	Sodium chloride

Water for injection purposes to make up to 2.0 ml

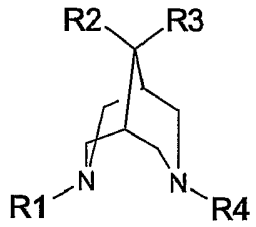
PREPARATION METHOD

Sodium chloride was dissolved in water for injection purposes. The active substance was added and dissolved while stirring. Sufficient water for injection purposes was added to make up the final volume. The mixture was passed through a 0.25 .mu. membrane filter. 2.15 ml aliquots were filled into brown glass ampoules, and the ampoules were hermetically closed. The ampoules were sterilized with steam for 30 minutes at 121 DEG C. 2 ml of the resulting injection solution contains 5 mg of the active substance.

Claims

1. The use of 3,7-diazabicyclo[3,3,1]nonane compounds, its physiologically acceptable acid addition salts and/or solvates thereof for the production of a pharmaceutical preparation for the treatment and/or prophylaxis of the Brugada syndrome and/or Brugada-related symptoms.

2. Use according to claim 1 wherein the 3,7-diazabicyclo[3,3,1]nonane compounds are corresponding to the Formula I:



I

wherein

R1 represents an alkyl group containing from 1 to 6 carbon atoms, an alkylene group containing from 3 to 6 carbon atoms having a double bond which is not linked directly to the nitrogen atom, a cycloalkylalkyl group containing from 4 to 9 carbon atoms, or a benzyl group,

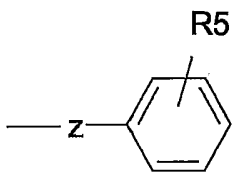
R2 represents a lower alkyl group, and

R3 represents a lower alkyl group, or

R2 and R3 together form an alkylene chain containing from 3 to 6 carbon atoms, and

R4 represents an alkyl group containing from 1 to 6 carbon atoms, an alkenyl group containing from 3 to 6 carbon atoms having a double bond which is not linked directly to the nitrogen atom, a cycloalkylalkyl group containing from 4 to 9 carbon atoms,

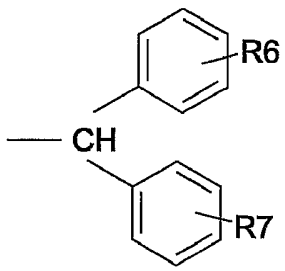
a group corresponding to the Formula a:



a

wherein
R5 represents hydrogen, halogen, lower alkyl or lower alkoxy, and
Z represents an alkylene chain containing from 1 to 3 carbon atoms or a propenylene chain having a double bond which is conjugated with the phenyl group, or

a group corresponding to the Formula b:



b

wherein
R6 represents hydrogen, halogen, lower alkyl or lower alkoxy, and
R7 represents hydrogen, halogen, lower alkyl or lower alkoxy,

or a physiologically acceptable acid addition salt and/or solvate thereof.

3. Use according to claim 1, wherein R1 represents an alkyl group containing from 1 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms.

4. Use according to claim 1, wherein R4 represents an alkyl group containing from 1 to 6 carbon atoms, a cycloalkylalkyl group containing from 4 to 7 carbon atoms, or a group corresponding to Formula b.

5. Use according to claim 1, wherein R1 represents an alkyl group containing from 3 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms, and R4 represents an alkyl group containing from 3 to 6 carbon atoms or a cycloalkylalkyl group containing from 4 to 7 carbon atoms.

6. Use according to claim 1, wherein said 3,7-diazabicyclo[3,3,1]nonane compound is a 9,9-alkylene-3,7-diazabicyclo[3.3.1]nonane compound of Formula I wherein R2 and R3 together form an alkylene chain containing from 4 to 5 carbon atoms, and R1 and R4 independently of one another each denote a straight-chain or branched

alkyl group of 3-4 carbon atoms or the cyclopropylmethyl group, and physiologically acceptable acid addition salts and/or solvates thereof.

7. Use according to claim 6, wherein said 3,7-diazabicyclo[3,3,1]nonane compound is a fumaric acid salt of said 9,9-alkylene-3,7-diazabicyclo[3.3.1]nonane compound containing 1.5 moles of fumaric acid per mole of compound of formula I.

8. Use according to claim 1, wherein said 3,7-diazabicyclo[3,3,1]nonane compound is selected from the group consisting of N,N'-dicyclopropylmethyl-9, 9-tetramethylen-3,7-diazabicyclo[3,3,1]nonane, N-isobutyl-N'-isopropyl-9,9-pentamethylen-3, 7-diazabicyclo[3,3,1]nonane, and physiologically acceptable acid addition salts and/or solvates thereof.

9. Use according to claim 8, wherein said 3,7-diazabicyclo[3,3,1]nonane compound is a fumaric acid salt of N,N'-dicyclopropylmethyl-9, 9-tetramethylene-3,7-diazabicyclo[3,3,1]nonane or of N-isobutyl-N'-isopropyl-9,9-pentamethylene-3, 7-diazabicyclo[3,3,1]nonane containing 1.5 moles of fumaric acid per mole of said 9,9-alkylene-3,7-diazabicyclo[3.3.1]-nonane compound.

10. The use according to any of the Claims 1, 5 and 7, wherein said 3,7-diazabicyclo[3,3,1]nonane compound is a hydrochloride salt.

11. Method of treatment and/or prophylaxis of the Brugada syndrome and/or Brugada-related symptoms characterized in that a 3,7-diazabicyclo[3,3,1]nonane compound corresponding to the Formula I as defined in one of the claims 1 to 10 is administered to a patient in need of such treatment and/or prophylaxis in an amount being effective to relieve, ameliorate and/or prevent said syndrome and/or symptoms.

12. Method of treatment and/or prophylaxis according to claim 11 characterized in that the 3,7-diazabicyclo[3,3,1]nonane compound is administered to a patient in need of such treatment and/or prophylaxis in an amount being effective to minimize and/or prevent the risk of sudden cardiac death and/or life-threatening ventricular arrhythmias.

13. Method of treatment and/or prophylaxis according to claim 11 characterized in that the patients in need of such treatment and/or prophylaxis are of male gender.

14. Method of treatment and/or prophylaxis according to claim 11 characterized in that the patients in need of such treatment and/or prophylaxis are infants and/or young children.

15. Method of treatment and/or prophylaxis according to claim 13 characterized in that the male Brugada syndrome or symptomatic patients are younger men, preferably younger men with life-threatening ventricular arrhythmias.

16. Method of treatment and/or prophylaxis according to one of the claims 11 to 15 characterized in that the 3,7-diazabicyclo[3,3,1]nonane compound is administered either as sole preventive medical drug treating, in particular where no ICD placement is available at all or right away, or adjuvant to ICD placement, in particular before and/or still after ICD placement.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/052310

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/439 A61K31/4995 A61P9/00 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)
IPC 7 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, PAJ, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTZELEVITCH C; BRUGADA, P; BRUGADA, J; BRUGADA, R; TOWBIN, J A; NADEMANEE, K: "Brugada Syndrome: 1992-2002 A Historical Perspective" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 41, no. 10, 21 May 2003 (2003-05-21), pages 1665-1671, XP002270528 cited in the application table 1 page 1670, column 1, line 11 - line 13 ----- -/--	1-16

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2005	24/01/2005

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/052310

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIEDRICHS, G S ET AL: "Tedisamil Attenuates Ventricular Fibrilation in a Conscious Canine Model of Sudden Cardiac Death" J CARDIOVASC PHARMACOL THERAPEUT, vol. 1, no. 4, 1996, pages 313-324, XP0009026151 abstract	1-16
X	ANTZELEVITCH, C; BRUGADA, P; BRUGADA, J; BRUGADA, R; SHIMIZU, W; GUSSAK, I; PEREZ RIERA, A R: "Brugada Syndrome: A Decade of Progress" CIRCULATION RESEARCH, vol. 91, no. 12, 2002, pages 1114-1118, XP002270529 cited in the application page 1116, column 2, line 18 - line 21	1-16
A	EP 0 550 383 A (KALI CHEMIE PHARMA GMBH) 7 July 1993 (1993-07-07) cited in the application abstract	1-16
A	EP 0 461 574 A (KALI CHEMIE PHARMA GMBH) 18 December 1991 (1991-12-18) cited in the application abstract	1-16
A	EP 0 103 833 A (KALI CHEMIE PHARMA GMBH) 28 March 1984 (1984-03-28) cited in the application abstract	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/052310

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-16
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/052310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0550383 A	07-07-1993	DE 4139763 A1	09-06-1993
		AT 124411 T	15-07-1995
		AU 652869 B2	08-09-1994
		AU 2981592 A	10-06-1993
		CA 2084489 A1	04-06-1993
		CN 1072931 A ,B	09-06-1993
		CZ 9203322 A3	11-08-1993
		DE 59202726 D1	03-08-1995
		DK 550383 T3	28-08-1995
		EP 0550383 A1	07-07-1993
		ES 2073900 T3	16-08-1995
		FI 925482 A	04-06-1993
		HK 1006568 A1	05-03-1999
		HU 63417 A2	30-08-1993
		HU 9400033 A3	30-01-1995
		IL 103819 A	12-09-1996
		JP 3180848 B2	25-06-2001
		JP 5247040 A	24-09-1993
		KR 252389 B1	01-05-2000
		LT 230 A	15-05-1994
		MX 9206988 A1	01-06-1993
		NO 924647 A	04-06-1993
		NZ 245227 A	27-06-1994
		SK 332292 A3	02-12-1998
		US 5324732 A	28-06-1994
		ZA 9208863 A	13-05-1993
EP 0461574 A	18-12-1991	DE 4019080 A1	19-12-1991
		AT 158583 T	15-10-1997
		AU 640236 B2	19-08-1993
		AU 7837791 A	19-12-1991
		CA 2044673 A1	16-12-1991
		DE 59108859 D1	30-10-1997
		DK 461574 T3	13-10-1997
		EP 0461574 A2	18-12-1991
		ES 2109244 T3	16-01-1998
		HU 58097 A2	28-01-1992
		JP 3086007 B2	11-09-2000
		JP 4230285 A	19-08-1992
		US 5164401 A	17-11-1992
EP 0103833 A	28-03-1984	DE 3234697 A1	22-03-1984
		AT 45579 T	15-09-1989
		AT 69817 T	15-12-1991
		AU 564910 B2	03-09-1987
		AU 1920683 A	22-03-1984
		CA 1254209 A1	16-05-1989
		CA 1259998 A2	26-09-1989
		CS 9103898 A3	15-07-1992
		DD 213923 A5	26-09-1984
		DE 3380409 D1	21-09-1989
		DE 3382466 D1	09-01-1992
		DK 422583 A ,B,	19-03-1984
		EP 0103833 A2	28-03-1984
		EP 0250903 A2	07-01-1988
		ES 8405398 A1	16-09-1984
		FI 833339 A ,B,	19-03-1984
		GR 78722 A1	02-10-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/052310

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0103833 A		HU	191096 B	28-01-1987
		IE	57580 B1	13-01-1993
		IL	69751 A	31-10-1986
		JP	1826596 C	28-02-1994
		JP	59070686 A	21-04-1984
		JP	1939319 C	09-06-1995
		JP	5247039 A	24-09-1993
		JP	6070056 B	07-09-1994
		LT	2012 R3	15-02-1993
		LV	5139 A3	10-06-1993
		MX	9202996 A1	01-07-1992
		NO	833346 A ,B,	19-03-1984
		NZ	205627 A	08-11-1985
		PH	20768 A	10-04-1987
		PT	77344 A ,B	01-10-1983
		SU	1272989 A3	23-11-1986
		US	4742172 A	03-05-1988
		US	4550112 A	29-10-1985
		ZA	8306185 A	25-04-1984