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Clarke, Modet & Cº

COLOMBIA

P-1186

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **04-086.386**
Solicitud de patente a nombre de **NOVARTIS AG.**

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN, actuando como apoderada sustituta de acuerdo con la sustitución adjunta, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **NOVARTIS AG**, domiciliada en Basilea Suiza, solicitante de la patente de la referencia, *interpongo recurso de reposición* contra la resolución No. 53683 emitida el 26 de octubre de 2009 por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente para la solicitud contenida en el expediente de la referencia.

1. FUNDAMENTOS DEL RECURSO

Mi mandante se permite manifestar a ese despacho que se reafirma en todos y cada uno de los argumentos que hacen pare integrante de la respuesta al oficio de fondo No. 14100 notificado por fijación en lista el 7 de noviembre de 2008.

En relación con los argumentos presentados por ese despacho en la resolución impugnada No. 53683, es necesario señalar que carecen de un enfoque adecuado de conformidad con las normas, jurisprudencia y reglas técnicas que existen para poder desvirtuar el nivel inventivo de la invención, toda vez que ese despacho no realizó un análisis apropiado de este requisito, dado que consideró que el problema técnico que subyace a la presente invención, ya había sido resuelto mediante las enseñanzas del documento D1 (WO0206253).

Lo anterior, claramente lleva a la Oficina de patentes a incurrir en un error adicional que es realizar un estudio de tipo hindsight, el cual no es permitido para la evaluación del nivel inventivo de la invención. Esto claramente conduce a esa oficina a una evaluación inadecuada de la altura inventiva de la solicitud en estudio, pues al no haber tenido en cuenta los lineamientos y la doctrina para realizar una apropiada evaluación de este requisito, efectúa una aplicación errónea de los artículos 16 y 18 de la Decisión 486, debido a que no tuvo en cuenta el estado de la técnica y no pudo demostrar cómo una persona medianamente versada en el campo técnico, habría llegado de manera evidente a partir del

documento citado a la materia objeto de la solicitud en estudio, es decir, que **su análisis fue incorrecto y producto de un enfoque retrospectivo de la materia divulgada en la invención en estudio**.

1.1 Violación de los artículos 14, y 18 de la Decisión 486 por una indebida aplicación de la norma basada en un error de interpretación de la misma.

Nivel inventivo

Ese despacho manifiesta en su resolución No. 53683 que: "*En el presente caso, el objeto carece de nivel inventivo porque el problema técnico que pretenden resolver ya había sido resuelto previamente...En efecto, el objeto de la solicitud, identificado en el numeral 1 de la presente resolución, se ve afectado por el documentos del estado de la técnica D1, tal como se muestra a continuación:"*(ver tabla página 4 a 6 de la resolución). Luego la Oficina de Patentes, manifiesta que:*"la diferencia de la solicitud con D1, es que la primera menciona para cada sal de caldio tetra, tri, mono y penta hidratadas, así como para cada sal de magnesio hexa, tetra, mono hidratadas, datos distintos de patrones de polvo de rayos X y/o de espectro ATR-IR.*
Sin embargo, la diferencia señalada, de la solicitud con D1, no concede un efecto técnico sorprendente, teniendo que cuanta que las formas cristalinas de las mismas sales, mencionadas en D1 (folio 245, renglones 6-8), ya presentaban las características de ser fáciles de manejar en los procesos de secado y granulación, para la preparación de formulaciones farmacéuticas, con lo cual se había resuelto el problema planteado en esta solicitud...."

En este orden de ideas, nos permitimos decir que el artículo 18 de la Decisión 486, indica que: "*Se considerará que una invención **tiene nivel inventivo**, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente **del estado de la técnica**.*" (El resaltado es nuestro).

Lo anterior significa que la referencia escogida por ese despacho en el examen de búsqueda, fue seleccionada partiendo del conocimiento de la invención en estudio **sin tener en cuenta cuál era el estado del arte en el momento de la fecha de prioridad reconocida de la solicitud en estudio**, es decir, antes del 4 de febrero de 2002, pues si bien el documento D1 que pertenece al mismo solicitante, fue publicado un mes antes de la fecha de prioridad de la presente solicitud, también es cierto que una persona medianamente versada en la materia no estaba en la capacidad de encontrar en el término de un mes el problema técnico que se plantea en esta solicitud, que ha venido solucionando el solicitante desde hace tiempo atrás.

En este sentido, es notable cómo ese Despacho viola el artículo 16 y 18 pues desconoce la altura inventiva de la presente invención frente a lo divulgado en el estado del arte justo antes de la presentación de prioridad de esta invención. También es claro, cómo la Superintendencia de Industria y Comercio no tuvo presente el significado de la expresión "**estado de la técnica**", pues tomando como punto de partida la misma invención, es decir, efectuando la búsqueda a *posteriori*, no realizó el esfuerzo intelectual de colocarse en la situación que habría tenido que confrontar una persona medianamente versada en la técnica en un momento en el que la presente invención no era conocida.

Esto se puede evidenciar cuando en la resolución No. 53683 se indica que: "*adicionalmente, y teniendo en cuenta que los hidratos que se pretenden reclamar, que tienen una caracterización de Rx y/o ATR-IR específica, no dan evidencia de alguna ventaja sobre los de D1, presentado la misma actividad como bloqueadores del receptor AT1 (capítulo descriptivo de la solicitud), se concluye que la materia reclamada no muestra altura inventiva.*"

Es claro entonces que la evaluación de la altura inventiva para el caso en concreto partió del mismo conocimiento de la solicitud en estudio, sin apreciar si las nuevas formas obtenidas para las sales de valsartan aquí reclamadas habrían sido obvias y susceptibles de derivación evidente a partir del documento D1. Adicionalmente, lo manifestado en la resolución impugnada hace referencia principalmente a que no hay datos que evidencien ventajas de las sales reclamadas sobre las encontradas en D1.

En ese orden de ideas, nos permitimos señalar que el documento D1 no le indica o sugiere a una persona medianamente versada en la materia la manera como se llegan a las sales de valsartan ahora reclamadas. De hecho, la simple mención de que se obtienen sales de valsartan en forma de cristales en D1, no significa que ya se hayan logrado todas las formas cristalinas de este compuesto. Aún más, el documento D1 no anticipa cuales serían las formas cristalinas que se podrían llegar a obtener en un futuro, simplemente porque no es posible predecir ni las condiciones en que un cristal se puede formar ni el cristal que se formará.

En ese orden de ideas, se hace necesario y pertinente dirigir la atención de ese despacho a la **Sentencia del 13 de agosto de 2009 para el expediente número 20003-00256 proferida por el Consejo de Estado en la Sala de lo contencioso administrativo sección primera**, principalmente a las páginas 24 a 31, donde se transcriben los apartes relevantes de la declaración del doctor **José Antonio Henao Martínez** en cuanto a la obtención de sales cristalinas de atorvastatina.

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En efecto, en dichos apartes se resalta el hecho de que "*...la obtención de una forma cristalina es algo bastante difícil, su grado de dificultad radica en que* ***no se tiene certeza de si un compuesto en particular puede cristalizar o no****, es importante cuando se inicia con el proceso de cristalización de una nueva forma cristalina establecer un conjunto de condiciones para ciertas variables las cuales permitan o favorezcan el proceso de cristalización.*"[1] (El resaltado es nuestro)

Basándonos en lo anterior, es claro que el nivel inventivo en esta clase de invenciones, radica en el establecimiento del conjunto de condiciones para las variables que permitan el proceso de cristalización por parte del inventor. Es más, resulta claro también que se requiere un gran esfuerzo por dicha persona para obtener una nueva forma cristalina. No en vano, en la sentencia antes mencionada también se establece que: "*...aún para un químico la obtención de una nueva forma cristalina es algo difícil,[...] el químico debe establecer las mejores condiciones de una serie de variables para que esa nueva forma cristalina llegue al estado sólido, por supuesto en forma ordenada; es importante también aquí resaltar que estas condiciones de esta nueva forma cristalina son* ***diferentes siempre a las condiciones establecidas para cristalizar otras formas cristalinas*** *del mismo compuesto químico.*"[2] (El resaltado es nuestro).

También es claro entonces que no basta con que se conozca en el estado del arte el concepto general de cristalización y recristalización, ni tampoco es suficiente conocer que existían en el estado de la técnica otros cristales para prever o predecir las condiciones de formación de nuevos cristales de dicho compuesto, toda vez que lo importante radica en la pericia del inventor en el establecimiento de las condiciones específicas para cristalizar un polimorfo determinado, ya que siempre serán distintas a las condiciones establecidas para la generación de otras formas cristalinas. De esto también se colige que el procedimiento para dicha obtención de formas cristalinas no puede ser estandarizado y mucho menos, se puede predecir qué nuevas formas de ordenamiento en el estado sólido dará un determinado compuesto, en nuestro caso, las sales de calcio del valsartan.

En este sentido, la declaración del testigo es contundente en afirmar que: "*...en el proceso de obtención de una nueva forma cristalina* ***por primera vez*** *no se sigue un procedimiento estándar similar a una receta, ya he mencionado que anteriormente para la obtención de esas condiciones que le favorezcan* ***se requiere nuevos procedimientos****, y juega un papel importante en la obtención de estas condiciones el investigador, él es la persona encargada de dar tanto las condiciones como el ambiente en el cual se van a ordenar esas moléculas al llegar al estado sólido.*"[3] (el resaltado es nuestro). Por consiguiente, debe

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[1] Sentencia del 13 de agosto de 2009 para el expediente número 20003-00256 proferida por el Consejo de Estado en la Sala de lo contencioso administrativo sección primera. Página 25, quinto párrafo.
[2] Op cit, página 25, sexto párrafo.
[3] Op cit, página 25 último párrafo y página 26 segunda línea.

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quedar claro que resulta errado pensar que porque en un documento se revelan sales cristalinas de un compuesto y se mencionen los solventes en los cuales se realizó un proceso de cristalización, se puede generalizar y estandarizar dicho proceso para volverlo un protocolo rutinario para producir todas las otras formas cristalinas que se puedan obtener de un compuesto a posteriori.

En efecto, el hecho de que se deban establecer las condiciones para cada nueva forma cristalina que se va a obtener por primera vez, no constituye un proceso rutinario en sí. Sobre este particular, el testigo experto también es claro en afirmar que: *"...la obtención de una nueva forma cristalina no se puede considerar como un acto rutinario, juega un papel importante* ***la creatividad del investigador****, es él quien tiene que establecer las mejores condiciones de esas variables para la obtención de esa nueva forma cristalina. Por lo tanto, para la obtención de diferentes formas cristalinas se requiere* ***diferentes condiciones****, las cuales* ***son dadas o impuestas por el investigador****."*[4] (El resultado es nuestro)

Así las cosas, se puede concluir que las características anteriormente vistas y expuestas en la Sentencia citada las comparte la presente invención, siendo aplicables estos criterios y no existiendo razón alguna para con base en el principio de igualdad, ese despacho aplique las mismas consideraciones y reconozca la altura inventiva de la presente solicitud. Las sales cristalinas de la presente invención son el producto de la actividad creativa del inventor quien mediante una serie de condiciones establecidas por él logra que las moléculas del ingrediente activo lleguen al estado sólido en una forma ordenada, jamás antes vista o reportada.

Ahora bien, en vista de la petición hecha por ese despacho en la resolución impugnada en cuanto a que no hay evidencia alguna de la ventaja de las sales reclamadas, es deseo del solicitante poner en consideración de esa oficina la patente estadounidense No. US 6,869,970, donde existen las suficientes pruebas de que las sales de valsartan reclamadas en la presente invención tienen un alto grado de disociación en agua y por lo tanto, una solubilidad en agua sustancialmente mejorada lo cual hace que sean estas formas ventajosas, puesto que el proceso de disolución es más rápido y se requerirá de una cantidad más pequeña de agua para tales soluciones, hechos que hacen que se incremente la biodisponibilidad biológica de las sales o hidratos de sales de valsartan, como así se expone en la columna 2 entre las líneas 48 a 58 de la patente estadounidense antes mencionada, de la cual nos permitimos adjuntar una copia informal.

[4] Op cit, página 26, cuarto párrafo.

> In addition, both the crystalline and the amorphous salts and salt hydrates according to the invention have a high degree of dissociation in water and thus substantially improved water solubility. These properties are of advantage, since on the one hand the dissolving process is quicker and on the other hand a smaller amount of water is required for such solutions. Furthermore, the higher water solubility can, under certain conditions, also lead to increased biological availability of the salts or salt hydrates in the case of solid dosage forms. Improved properties are beneficial especially to the patients.

Aún más, en dicho documento también se pone de manifiesto que se ha probado que la formación de sales e hidratos de sales de valsartan con propiedades ventajosas deseadas resulta ser difícil ya que en la mayoría de los casos, por ejemplo, se obtienen sales amorfas con poca estabilidad, tal como formas de espuma dura, ceras y aceites. Por lo cual, se ha encontrado que las sales y los hidratos de sales de valsartan resultan ser particularmente ventajosas cuando se comparan con la forma libre del ácido de valsartan. Esto lo manifiesta el solicitante desde la línea 66 de la columna 1 hasta la línea 6 de la columna 2 del documento US 6,869,970.

En resumen, las sales e hidratos de las sales de valsartan reclamadas en la solicitud en estudio, muestran ventajas importantes sobre la forma ácida del valsartan, lo cual ratifica que con dichas sales se puede obtener un mejor manejo en los procesos de secado y granulación, pues gracias a que no son formas de espuma dura, ceras o aceites, permiten que sean de fácil manejo a la hora de realizar dichos procesos. Estas ventajas no habían sido reportadas o sugeridas en el documento D1, por lo cual, una persona medianamente versada en la materia técnica no habría encontrado evidente las sales y los hidratos de las sales de valsartan reclamadas en la solicitud en estudio.

Así las cosas, me permito decir que los argumentos mostrados por ese despacho en su resolución no fueron el resultado de una evaluación apropiada y objetiva de las características técnicas de la invención en estudio justo antes de la existencia y conocimiento de la misma. Por lo tanto, solicito de manera atenta se tengan en cuenta los argumentos anteriores.

2. Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

a) Que de conformidad con lo previsto por los artículos 3 (inciso 3); 35 (inciso 2) y 59 (inciso 2) del Código Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de este recurso.

b) Que se revoque la resolución No. 53683 emitida el 26 de octubre de 2009 expedida por el Superintendente de Industria y Comercio, y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante.

Señor Superintendente,

DILIA RODRIGUEZ D´ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.

/srr

PRESENTACION PERSONAL

El anterior escrito fue presentado ante el

NOTARIO ONCE DEL CIRCULO DE BOGOTA, D.C.

personalmente por Oliver Rodriguez

El interesado

quien exhibió la c.c. 4664682 Bogota

y Tarjeta Profesional No. 20824 C.S.J.

Fecha 26 NOV 2009

Guillermo Chávez Cristancho

NOTARIO

REPUBLICA DE COLOMBIA

Guillermo Chávez Cristancho

NOTARIA 11 DEL CIRCULO DE BOGOTA, D.C.

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Clarke, Modet & Cº

COLOMBIA

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF: Expediente : **04-086.386**

Solicitante : **Novartis AG.**

Yo, **JIMENA ESCOBAR URIBE,** identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53 Piso 6, atentamente digo a usted que sustituyo el poder con que obro a la doctora **DILIA RODRIGUEZ D´ALEMAN**, domiciliada en Bogotá, D.C., portadora de la tarjeta profesional No. 20.824, con las mismas facultades con que me fueron conferidas para este caso.

JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquén
T.P. 68.228

Acepto sustitución

DILIA RODRIGUEZ D´ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20.824

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PRESENTACION PERSONAL

El anterior escrito fue presentado ante el

NOTARIO ONCE DEL CIRCULO DE BOGOTA, D.C.

personalmente por Jimena Escobar Uribe

quien exhibió la C.C. 39771452 Usaquen

y Tarjeta Profesional No. 68226

Fecha 1 OCT 2009

1 OCT 2009

NOTARIO

US006869970B2

(12) **United States Patent**
Marti

(10) **Patent No.: US 6,869,970 B2**
(45) **Date of Patent: Mar. 22, 2005**

(54) **CRYSTALLINE SALT FORMS OF VALSARTAN**

(75) Inventor: **Erwin Ernst Marti**, Basel (CH)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/353,389**

(22) Filed: **Jan. 29, 2003**

(65) **Prior Publication Data**

US 2003/0171414 A1 Sep. 11, 2003

Related U.S. Application Data

(60) Provisional application No. 60/354,199, filed on Feb. 4, 2002.

(51) **Int. Cl.**[7] **A61K 31/41**; C07D 257/04

(52) **U.S. Cl.** **514/381**; 548/253

(58) **Field of Search** 548/253; 514/381

(56) **References Cited**

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* cited by examiner

Primary Examiner—Rita Desai
Assistant Examiner—Robert Shiao
(74) *Attorney, Agent, or Firm*—Gregory D. Ferraro

(57) **ABSTRACT**

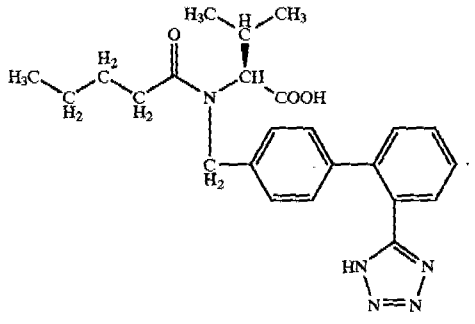
The invention relates to new forms of salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and usage, and pharmaceutical preparations containing such a salt.

23 Claims, No Drawings

CRYSTALLINE SALT FORMS OF VALSARTAN

The invention relates to additional new salts and salt hydrates of the AT_1 receptor antagonist (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amine (valsartan) of formula

(I)



The active ingredient valsartan is the free acid which is described specifically in EP 0443983, especially in example 16; it has two acidic hydrogen atoms: (i) the hydrogen atom (H atom) of the carboxyl group, and (ii) that of the tetrazole ring. Accordingly, one acidic H atom (primarily the carboxyl H atom) or both acidic H atoms may be replaced by a monovalent or higher valent, e.g. divalent, cation. Mixed salts may also be formed.

EP 443983 does not disclose any specific salts or salt solvates, e.g. hydrates, of valsartan. Also, it does not mention any special properties of salts or salt solvates, e.g. hydrates. Meanwhile, the active ingredient valsartan has been introduced as an anti-hypertensive agent in a series of countries under the trade name DIOVAN.

The free acid valsartan has a melting point in a closed crucible of 80 to 95° C. and in an open crucible of 105 to 110° C. and a melting enthalpy of 12 kJ/mol. The specific optical rotation is $[\alpha]^{20}_D=(-70\pm2)^0$ measured for a concentration of c=1% in methanol.

The density of the valsartan crystals and of the salt hydrates was determined by a helium pycnometer (Accupyc 1330 of Micromeritics, Norcross, Ga., USA). The density for the crystals of the free acid valsartan is 1.20±0.02.

The X-ray diffraction diagram consists essentially of a very broad, diffuse Xray reflection; the free acid is therefore characterised as almost amorphous under X-ray. The melting point linked with the measured melting enthalpy of 12 kJ/mol unequivocally confirms the existence of a considerable residual arrangement in the particles or structural domains for the free acid valsartan.

There is a need for more stable, e.g. crystalline forms of valsartan, which, for example, are even easier to manage in the drying or grinding processes following the final stage of the chemical preparation process, and also in the steps for preparing the pharmaceutical formulations and lead to an improvement of the process for the manufacture of the drug substance. Many futile attempts have been made to find improved forms through salt formation, the forms ideally being as crystalline as possible, as well as physically and chemically stable. Only the salts according to the present invention including both of the substances assigned here as starting materials, there solvates, e.g. hydrates and polymorphous forms thereof exhibit the desired improved properties.

The formation of salts and salt hydrates of valsartan with the desired advantageous properties has proved to be difficult. In the majority of cases, for example, amorphous salts with little stability are obtained (such as hard foams, waxes or oils). Extensive research has shown that the additional salts and salt hydrates of valsartan according to the invention have proved to be particularly advantageous compared with the free acid valsartan.

The objects of the present invention are salts and salt hydrates of valsartan which are selected from the group of earth alkalimetals consisting of the magnesium salt and the calcium salt, as well as salt mixtures, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof, the respective production and use, and pharmaceutical preparations containing such salts.

Salt mixtures are (i) single salt forms from different cations selected from the above group or (ii) mixtures of those single salt forms which exist for example in the form of conglomerates or (III) mixtures of a single salt or a salt hydrate consisting of different physical phases such as several polymorphic forms, of different hydrates or also the anhydrate, of different amorphous forms or (IV) mixtures of any form listed under (I), (II), and (III) with each other.

Preferred salts are for example selected from the calcium salt of valsartan in crystalline and amorphous forms, especially in hydrate form, primarily the tetrahydrates, the trihydrates, the monohydrate, the di-(calcium salt of valsartan) pentahydrate, the anhydrate, the amorphous forms thereof; magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrates, the trihydrates, the monohydrate, the anhydrate, the amorphous forms thereof.

The salts according to the invention preferably exist in isolated and essentially pure form, for example in a degree of chemical purity of >95%, preferably >98%, primarily >99%. The enantiomer purity of the salts according to the invention is >98%, preferably >99%.

Compared with the free acid, the salts according to the invention, or the amorphous forms, solvates such as salt hydrates, and also the corresponding polymorphous forms thereof, have unexpectedly advantageous properties. Under given conditions, the crystalline salts and crystalline salt hydrates have a clear melting point which is linked with a marked, endothermic melting enthalpy. The crystalline salts, salt hydrates, amorphous forms and mixtures thereof according to the invention have limited stability, i.e. as the solid, they have a restricted stability range. To be stabilised, they require certain measures which can be achieved for example by galenic formulations.

In addition, both the crystalline and the amorphous salts and salt hydrates according to the invention have a high degree of dissociation in water and thus substantially improved water solubility. These properties are of advantage, since on the one hand the dissolving process is quicker and on the other hand a smaller amount of water is required for such solutions. Furthermore, the higher water solubility can, under certain conditions, also lead to increased biological availability of the salts or salt hydrates in the case of solid dosage forms. Improved properties are beneficial especially to the patients.

The high crystallinity of certain salt hydrates allows the use of a choice of analytical methods, especially the various X-ray methods and/or the infrared spectrum preferably by means of ATR-IR (Attenuated Total Reflection-Infrared Spectroscopy), the usage of both methods permit a clear and simple analysis of their release to be made. This factor is also of great importance to the quality of the active substance and its galenic forms during production, storage and administration to the patients.

The invention accordingly relates to crystalline, also partly crystalline and amorphous salts or salt hydrates of valsartan.

As well as the solvates, such as hydrates, the invention also relates to polymorphous forms of the salts according to the invention.

Solvates and also hydrates of the salts according to the invention may be present, for example, as mono-, di-, tri-, tetra-, penta-, hexa-solvates or hydrates, respectively. Solvates and hydrates may also be consisting in stoichiometric ratios for example, with two, three, four salt molecules per solvate or per hydrate molecule. Another possibility for example, that two salt molecules are stoichiometric related to three, five, seven solvent or hydrate molecules. Solvents used for crystallisation, such as alcohols, especially methanol, ethanol, aldehydes, ketones, especially acetone, esters, e.g. ethyl acetate, may be embedded in the crystal grating. Preferred are pharmaceutically acceptable solvents. The extent to which a selected solvent or water leads to a solvate or hydrate in crystallisation and in the subsequent process steps or leads directly to the free acid is generally unpredictable and depends on the combinations of process conditions and the various interactions between valsartan and the selected solvent, especially water. The respective stability of the resulting crystalline or amorphous solids in the form of salts, salt solvates or salt hydrates, must be determined by experimentation. It is thus not possible to focus solely on the chemical composition and the stoichiometric ratio of the molecules in the resulting solid, since under these circumstances both differing crystalline solids and differing amorphous substances may be produced.

The description salt hydrates for corresponding hydrates may be preferred, as water molecules in the crystal structure are bound by strong intermolecular forces and thereby represent an essential element of structure formation of these crystals which, in part, are extraordinarily stable. However, water molecules are also existing in certain crystal lattices which are bound by rather weak intermolecular forces. Such water molecules are more or less integrated in the crystal structure forming, but to a lower energetic effect. The water content in amorphous solids can, in general, be clearly determined, as in crystalline hydrates, but is heavily dependent on the drying and ambient conditions. In contrast, in the case of stable hydrates, there are clear stoichiometric ratios between the pharmaceutical active substance and the water. In many cases these ratios do not fulfil completely the stoichiometric value, normally it is approached by lower values compared to theory because of imperfection or of certain crystal defects. The ratio of organic molecules to water molecules for the weaker bound water may vary to a considerable extend, for example, even extending from the anhydrous form over mono-, di-, tri- or tetra-hydrates. On the other hand, in amorphous solids, the molecular structure classification of water is not stoichiometric; the classification may however also be stoichiometric only by chance.

In some cases, it is not possible to classify the exact stoichiometry of the water molecules, since layer structures form, e.g. in the alkali metal salts, especially in the potassium salt, so that the embedded water molecules cannot be determined in defined form.

For the crystalline solids having identical chemical composition, the different resulting crystal gratings are summarised by the term polymorphism.

Any reference hereinbefore and hereinafter, to the salts according to the invention is to be understood as referring also to the corresponding solvates, such as hydrates, and polymorphous modifications, and also amorphous forms, as appropriate and expedient.

The particularly preferred salt hydrate is the tetrahydrate of the calcium salt of valsartan in the polymorphic form $A_{1,Ca}$. In a closed specimen container, for a heating rate of T_r=10 K·min^{-1} it has a melting point of 191±1.5° C. and a melting enthalpy of 77±4 kJ.Mol^{-1}. The tetrahydrate of the calcium salt of valsartan $A_{1,Ca}$ is not stable at the melting point both in respect of the hydrate water and therefore in respect of the chemical and physical structure of the molecule. The indicated melting point is a hydrate melting point which can only be measured in a closed specimen container. Gold containers with a wall thickness of 0.2 mm were used; after weighing in samples of between 2 and 4 mg salt hydrate, they were sealed by cold welding. These gold containers have an internal free volume of ca. 22 microliters. The amounts of the sample and the volume of the pressurised containers must be suitably adapted, so that strong dehydration of the salt hydrates cannot take place during measurement of the melting point. The partial pressure of the water at 191° Celsius is ca. 13 bar, so that with an open container in DSC (Differential Scanning Calorimeter) during measurement of the melting point, conversion to the anhydrate takes place. Both the high hydrate melting point and the amount of the melting enthalpy are an expression of the exceptional stability of the crystal lattice of the form $A_{1,Ca}$ of the tetrahydrate of the calcium salt of valsartan. These two thermodynamic characteristics illustrate the advantageous physical properties, compared to the free acid, with the two corresponding data, namely a melting point in the closed system of 90° C. and a melting enthalpy of 12 kJ.Mol^{-1}. These thermodynamic data, together with the X-ray data, prove the high stability of this crystal lattice. They are the base for the special physical and chemical resistance of the tetrahydrate of the calcium salt of valsartan of the polymorphic form $A_{1,Ca}$.

Measurement of the infrared spectrum likewise took place by means of ATR-IR (Attenuated Total Reflection-Infrared Spectroscopy) using the instrument Spektrum BX from Perkin-Elmer Corp., Beaconsfield, Bucks, England. The tetrahydrate of the calcium salt of valsartan $A_{1,Ca}$ has the following absorption bands expressed in reciprocal wave numbers (cm^{-1}): 3594 (w); 3307 (w); 3056 (w); 2960 (m); 2871 (w); 1621 (st); 1578 (st); 1459 (m); 1442 (m); 1417 (m); 1407 (m); 1364 (m); 1357 (m); 1319 (m); 1274 (m); 1242 (w); 1211 (m); 1180 (m); 1149 (w); 1137 (m); 1105 (m); 1099 (m); 1012 (m); 1003 (m); 974 (m); 965 (w); 955 (w); 941 (w); 863 (w); 856 (w); 844 (m); 823 (m); 791 (m); 784 (m); 758 (m); 738 (st); 698 (m). The intensities of the absorption bands are indicated as follows: (w)=weak; (m)= medium and (st)=strong intensity. The characteristic absorption bands of the ATR-IR spectroscopy for the polymorphic form $A_{1,Ca}$ of the tetrahydrate of the calcium salt of valsartan are shown by the following values expressed in reciprocal wave numbers (cm^{-1}): 3307 (w); 2960 (m); 1621 (st); 1578 (st); 1459 (m); 1442 (m); 1417 (m); 1407 (m); 1364 (m); 1357 (m); 1319 (m); 1274 (m); 1211 (m); 1180 (m); 1137 (m); 1012 (m); 1003 (m); 974 (m); 758 (m); 738 (st); 698 (m). The error margin for all absorption bands of ATR-IR is ±2 cm^{-1}.

The water content is in theory 13.2% for the tetrahydrate of the calcium salt of valsartan. Using the thermobalance TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA) the water content was determined for the polymorphic form $A_{1,Ca}$ between 20° C. and 225° C. as 12.4%. A total formula was calculated from this $(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}\cdot(3.8\pm0.2)$ H_2O.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the tetrahydrate of the

calcium salt of valsartan $A_{1,Ca}$ as a function of temperature, was measured at a heating rate of 10 K·min^{-1}. The results are illustrated in table 1.

TABLE 1

temperature [° C.]	weight loss or water loss in %
25	1.0 ± 0.1
50	2.9 ± 0.2
75	5.4 ± 0.5
100	10.0 ± 0.5
125	12.2 ± 0.3
150	12.8 ± 0.3
175	13.1 ± 0.3
200	13.3 ± 0.3
225	13.4 ± 0.3
250	13.5 ± 0.3
275	13.7 ± 0.3

An essential feature for the quality of a pure active substance both for the physical-chemical procedures such as drying, sieving, grinding, and in the galenic processes which are carried out with pharmaceutical excipients, namely in mixing processes, in granulation, in spray-drying, in tabletting, is the water absorption or water loss of this active substance depending on temperature and the relative humidity of the environment in question. With certain formulations, free and bound water is without doubt introduced with excipients and/or water is added to the process mass for reasons associated with the respective formulation process. In this way, the pharmaceutical active substance is exposed during the production and galenic processes over time periods of up to several hours or even days to free water of different activity (partial vapour pressure) which is mainly depending on temperature. However, it is easily possible to reach a well-defined hydrate form in the production of the activity substance as well as in the formulation of a salt of valsartan after a certain equilibration time under rather constant conditions in respect to temperature and to the relative humidity.

Further characterisation of the tetrahydrate of the calcium salt of valsartan is effected using the interlattice plane intervals determined by a X-ray powder pattern. Measurement of the X-ray powder patterns was made with a Guinier camera (FR 552 from Enraf Nonius, Delft, NL) on a X-ray film in transmission geometry, using Cu—Ka_1 radiation at room temperature. Evaluation of the films for calculation of the interlattice plane intervals is made both visually and by a Line-Scanner (Johansson Täby, S), and the reflection intensities are determined simultaneously. The preferred characterisation of the tetrahydrate of the calcium salt of valsartan $A_{1,Ca}$ is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values are indicated with the appropriate error limits.

The intensities are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.2±0.3(vst), 11.4±0.2(vw), 9.9±0.2(w), 9.4±0.2(vw), 8.06±0.1(vw), 7.73±0.1(vw), 7.05±0.1(vw), 6.50±0.05(vw), 6.36±0.05 (vw), 5.82±0.05(w), 4.94±0.05(vw), 4.73±0.05(vw), 4.33 0.05(vw), 4.17±0.05(vw), 4.13±0.05(vw), 3.93±0.05(vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 16.2±0.3, 11.4±0.2, 9.9±0.2, 9.4±0.2, 8.06±0.1, 7.05±0.1, 6.50±0.05, 5.82±0.05, 4.94±0.05, 4.73±0.05, 4.33±0.05, 4.17±0.05, 4.13±0.05, 3.93±0.05.

Another polymorphic form of the tetrahydrate of the calcium salt of valsartan is the solid state form $A_{2,Ca}$. The melting point of form $A_{2,Ca}$ is 195±1.5° C. and the melting enthalpy is 98±5 kJ.Mol^{-1}. The indicated melting point is a hydrate melting point which can only be mesured in a closed specimen container. Gold containers are used and sample weights of between 2 and 4 mg salt hydrate. The heating rate applied is T_r=10 K·min^{-1}. For details see the explanations given for the form $A_{1,Ca}$. The tetrahydrate of the calcium valsartan salt $A_{2,Ca}$ reveals the following loss of water as a function of temperature using the thermogravimetric instrument TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA) with a heating rate of 10 K·min^{-1}, in a water-free N_2 atmosphere, the weight loss is illustrated in Table 2.

TABLE 2

temperature [° C.]	weight loss or water loss in %
25	0 ± 0.1
50	0.1 ± 0.1
75	0.7 ± 0.2
100	4.9 ± 0.4
125	11.2 ± 0.3
150	12.2 ± 0.3
175	12.6 ± 0.3
200	12.7 ± 0.3
225	12.8 ± 0.3
250	12.9 ± 0.3
275	13.1 ± 0.3

The theoretical water content is for a tetrahydrate of the calcium salt of valsartan 13.2%. The tetrahydrate of the form $A_{2,Ca}$ has a bound water content at 225° C. determined as a weight loss of 12.8% and the total formula is calculated from this $(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}\cdot(3.9\pm0.2)\ H_2O$.

A solid state characterization of the calcium salt of valsartan in form of the tetrahydrate $A_{2,Ca}$ is achieved by a X-ray powder pattern and by the evaluation of the reflections into the interlattice plane intervals. The measurements are throughout made without specific explanations with a Guinier camera (FR 552 from Euraf Nonius, Delft, NL) on an X-ray film in transmission geometry, using Cu—Ka_1 radiation at room temperature. Evaluation of the films for calculation of the interlattice plane intervals is made both visually and by a line scanner (Johansson, Täby, S), and the reflection intensities are determined simultanously. The preferred characterization of the tetrahydrate of the calcium salt of valsartan $A_{2,Ca}$ is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, values are indicated with the appropriate error limits. The intensities are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.2±0.3(vst), 9.9±0.2(w), 9.4±0.2(vw), 8.05±0.1(vw), 7.72±0.1(vw), 7.04±0.1(vw) 6.49±0.05(w), 6.35±0.05(vw), 5.82±0.05(w), 4.94±0.05(vw), 4.73±0.05(vw), 4.34±0.05 (vw), 4.13±0.05(m), 3.93±0.05(w), 3.30±0.05(vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 16.2±0.3, 9.9±0.2, 9.4±0.2, 8.05±0.1, 7.04±0.1, 6.49±0.05, 5.82±0.05, 4.94±0.05, 4.13±0.05, 3.93±0.05.

A new substance has been found as polymorphic form of a trihydrate of the calcium salt of valsartan assigned with $B_{1,Ca}$. The melting point of the substance $B_{1,Ca}$ is measured in a closed sample cell with a heating rate of 10 K·min^{-1} as T_{fus}=175±2° C. and the melting enthalpy of the partially crystalline sample is 12 kJ.Mol^{-1}. The water content is in theory 10.24% for the trihydrate of the calcium salt of valsartan. Using the thermogravimetric instrument TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA) the water con-

tent was determined for the polymorphic form $B_{1,Ca}$ as 9.9±0.4%. A total formula was calculated from this polymorphic form of the trihydrate of the calcium salt of valsartan $(C_{24}H_{27}N_2O_3)^{2-}Ca^{2+}\cdot(2.9\pm0.3)\ H_2O$.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the trihydrate of the calcium salt of valsartan in the polymorphic form $B_{1,Ca}$ as a function of temperature, was measured at a heating rate of 10 $K\cdot min^{-1}$. The results are illustrated in table 3.

TABLE 3

temperature [° C.]	weight loss or water loss in %
25	0.4 ± 0.1
50	2.0 ± 0.3
75	4.0 ± 0.4
100	6.3 ± 0.4
125	8.5 ± 0.4
150	9.5 ± 0.4
175	9.7 ± 0.4
200	9.9 ± 0.4
225	9.9 ± 0.4
250	10.0 ± 0.4
275	10.3 ± 0.4

A solid state characterization of the trihydrate of the calcium salt of valsartan $B_{1,Ca}$ is preferably performed by X-ray powder patterns with the evaluation of the interlattice plane intervals. The measurements have been performed with two samples of the trihydrate $B_{1,Ca}$ of the calcium salt of valsartan and with two different instruments. The first instrument used was a temperature-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL, equipped with a low and medium temperature attachement from Anton Paar GmbH, A-8054 Graz, Austria. The second instrument is a powder diffractometer PW 1710 also from Philips Analytical X-ray, 7602 Almelo, NL. Two parallel measurements with a reference sample, namely a tetrahydrate of the calcium salt of valsartan have been used to calibrate the powder diffractometer PW 1710 with a Guinier camera (FR 552 from Enraf Nonius, Delft, NL) on a X-ray film in transmission geometry, using Cu—Ka_1 radiation. The corrections for the interlattice plane intervals to reach the values of the Guinier camera from the powder diffractometer PW1710 were ranging from +0.55 Å for a d-value of 16 Å to +0.02 Å for a d-value of 5.7 Å. No correction was necessary for lower d-values. The characterization of the trihydrate of the calcium salt of valsartan $B_{1,Ca}$ with the interlattice plane intervals d is as such, whereby, in the following values are indicated with the appropriate error limits. The intensities of the d-values are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.0±0.3(vst), 11.4±0.2(m), 10.0±0.2(vw), 9.4±0.2 (vw), 9.1±0.2(vw), 8.06±0.1(vw), 7.75±0.1(vw), 7.03±0.1 (vw), 6.48±0.05(vw), 6.10±0.05(vw), 5.76±0.05(vw), 5.16±0.05(vw), 4.95±0.05(vw), 4.75±0.05(vw), 4.68±0.05 (vw), 4.33±0.05(vw). The characteristic reflections in the X-ray diffraction diagram reveal the following interlattice plane intervals for the form $B_{1,Ca}$: d in [Å]: 16.0±0.3, 11.4±0.2, 10.0±0.2, 9.4±0.2, 8.06±0.1, 7.75±0.1, 7.03±0.1, 6.48±0.05, 6.10±0.05, 5.16±0.05, 4.75±0.05.

The new polymorphic form $B_{2,Ca}$ of a trihydrate of the calcium salt of valsartan has a melting point of 197±1.5° C. measured in a closed sample cell with a Pyris 1 DSC (Differential Scanning Calorimeter) from Perkin-Elmer Corp., Norwalk, Conn. USA. The enthalpy of fusion has been determined also from a DSC curve measured also with a heating rate of 10 $K\cdot min^{-1}$ as 62±5 $kJ.Mol^{-1}$. During the DSC measurements of the melting of the trihydrate $B_{2,Ca}$ of the calcium salt of valsartan also a glass transition was observed, as an unequivocal proof of amorphous substance present in this substance. The glass transition temperature was calculated with T_g=66±15° C. as the mid point of a change of the specific heat of the substance, namely the trihydrate $B_{2,Ca}$ of the calcium salt of valsartan. The value for the change of the specific heat was calculated as Δc_p= $0.10\pm0.03 J\cdot(g\cdot K)^{-1}$. The amorphicity present in the substance $B_{2,Ca}$ approximated by this value for the change of the specific heat is 18±5%. The crystalline trihydrate $B_{2,Ca}$ of the calcium salt of valsartan is according to the heat of fusion measured with the DSC Pyris 1, the main component is this crystalline product, the amorphous part of the calcium salt of valsartan is a minor part.

The water content of the trihydrate $B_{2,Ca}$ of the calcium salt of valsartan is 10.5±0.5%. The value was measured with a thermogravimetric instrument TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The total formula was calculated from this bound water content for the polymorph of the trihydrate $B_{2,Ca}$ as $(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}\cdot(3.1\pm0.3)H_2O$.

Water may also be present in the amorphous part of the substance $B_{2,Ca}$, which is depending on the concentration of the non-crystalline part. This water is within the amorphous part differently bound compared to the water molecules in the hydrate form of the crystalline part. As a first approximation one can state, that the crystalline and the amorphous part are similar in the water concentration in case the last process of reaching the state of the material is not passing the anhydrous form of the calcium salt of valsartan. The explanation for this fact is given with the molecular structure of the calcium salt of valsartan, the same holds for the magnesium salt of valsartan, namely that the salt structure is to a considerable part based on the short range order of the molecular interacting substances valsartan, calcium or magnesium and water which is not free water, however structural bound water. This narrow range molecular structure is rather similar for the crystalline part as for the amorphous part. Of course, in the amorphous material, there is a complete lack of long range order in contrary to the crystalline material were any molecule, in the present case, any molecle in trihydrate $B_{2,Ca}$ calcium salt of valsartan is over neighboring molecules structural interrelated with all the molecules within any single crystal.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the trihydrate $B_{2,Ca}$ as a function of temperature, was measured at a heating rate of 10 $K\cdot min^{-1}$. The results for the polymorph $B_{2,Ca}$ of the trihydrate of the calcium salt of valsartan are illustrated in table 4.

TABLE 4

Temperature [° C.]	Weight loss or water loss in %
25	0.1 ± 0.05
50	0.9 ± 0.1
75	2.2 ± 0.4
100	5.8 ± 0.4
125	8.9 ± 0.4
150	9.9 ± 0.4
175	10.2 ± 0.4
200	10.3 ± 0.4
225	10.5 ± 0.4
250	10.5 ± 0.4
275	10.8 ± 0.4

The solid state characterization of the trihydrate of the calcium salt of valsartan $B_{2,Ca}$ was performed by X-ray

powder spectroscopy using two different instruments and two different charges produced with evaluation of the interlattice plane intervals. The first instrument was a powder diffractometer PW 1710 from Philips Analytical X-ray, 7602 Almelo, NL. The second instrument was a Guinier camera FR 552 from Enraf Nonius, Delft, NL on a X-ray film in transmission geometry, using Cu—Ka_1 radiation. The first instrument has been calibrated with the Guinier camera, the corrections ranging from +0.55 Å for a d-value of 16 Å to +0.02 Å for a d-value of 5.7 Å. No corrections were necessary for lower d-values. The characterization of the trihydrate of the calcium salt of valsartan $B_{2,Ca}$ with the interlattice plane intervals is as such, whereby, in the following values are indicated with the appropriate error limits. The intensities of the d values are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.2±0.3 (vst), 11.5±0.2(w), 9.9±0.2(w), 9.4±0.2(w), 9.0±0.1(vw), 8.13±0.1(vw), 7.78±0.1(vw), 7.04±0.1(vw), 6.50±0.1(vw), 6.09±0.05(vw), 5.79±0.05(vw), 5.18±0.05(vw), 4.95±0.05 (vw), 4.74±0.05(vw), 4.16±0.05(w), 3.96±0.05(vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 16.2±0.3, 11.5±0.2, 9.9±0.2, 9.4±0.2, 7.04±0.1, 6.50±0.1, 5.79±0.05, 4.74±0.05, 4.16±0.05, 3.96±0.05.

Another polymorph of the trihydrate of the calcium salt of valsartan namely the $B_{3,Ca}$ has a melting point measured with a heating rate of 10K·min^{-1} in a hermetically sealed sample cell of 192±1.5° C. The enthalpy of fusion has been determined also by a DSC measurement with 51 kJ.Mol^{-1}.

The water content of the polymorphic form $B_{3,Ca}$ for the trihydrate of the calcium salt of valsartan was determined with a thermobalance from Perkin-Elmer Corp., Norwalk, Conn. USA, named TGS-2 with a value of 9.8±0.5%. The total formula was calculated from this bound water content for the polymorphic from $B_{3,Ca}$ with $(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}\cdot(2.9\pm0.2)H_2O$.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the trihydrate $B_{3,Ca}$ as a function of temperature, was measured at a heating rate of 10 K·min^{-1}. The results for the polymorphic form $B_{3,Ca}$ of the trihydrate of the calcium salt of valsartan are illustrated in table 5.

TABLE 5

temperature [° C.]	weight loss or water loss in %
25	0.3 ± 0.1
50	1.4 ± 0.2
75	2.8 ± 0.4
100	5.7 ± 0.4
125	8.4 ± 0.4
150	9.4 ± 0.4
175	9.6 ± 0.4
200	9.7 ± 0.5
225	9.8 ± 0.5
250	10.0 ± 0.5
275	10.2 ± 0.5

The Guinier camera FR552 with a X-ray film in transmission geometry, using a Cu—Ka_1 radiation from Enraf Nonius, Delft, NL has been installed to characterize at room temperature the crystal lattice by the interlattice plane intervals of the calcium salt of valsartan in form of the trihydrate $B_{3,Ca}$.

The reflections in the X-ray diffraction diagram for the trihydrate of the calcium salt of valsartan $B_{3,Ca}$ reveal the following interlattice plane intervals d, whereby, values are indicated with the appropriate error limits. The intensities of the d-values are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.1±0.3(vst), 11.4±0.2(m), 9.9±0.2(w), 9.4±0.2(w), 9.0±0.1(vw), 8.04±0.1(vw), 7.73±0.1(vw), 7.03±0.1(vw), 6.47±0.05(vw), 6.33±0.1(vw), 6.09±0.05(vw), 5.79±0.05(w), 5.17±0.05(vw), 4.95±0.05 (vw), 4.73±0.05(vw), 4.48±0.05(vw), 4.33±0.05(vw), 4.15±0.05(vw), 4.11±0.05(vw), 3.94±0.05(vw), 3.61±0.05 (vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 16.1±0.3, 11.4±0.2, 9.9±0.2, 9.4±0.2, 9.0±0.1, 7.03±0.1, 6.47±0.05, 5.79±0.05, 4.15±0.05, 3.94±0.05.

Measurements of the infrared spectrum were performed by means of ATR-IR (Attenuated Total Reflection-Infrared Spectroscopy) using the instrument Spektrum BX from Perkin-Elmer Corp., Beaconsfield, Bucks, England. The trihydrate of the calcium salt of valsartan $B_{3,Ca}$ has the following ATR-IR adsorption bands expressed in reciprocal wave numbers (cm^{-1}): 3594(w); 3309(w); 3053(w); 2959 (w); 2930(w); 2870(w); 1621(m); 1577(m); 1505(w); 1458 (m); 1416(m); 1405(m); 1354(w); 1301(w); 1273(w); 1210 (w); 1179(w); 1138(w); 1104(w); 1099(w); 1012(w); 1003 (w); 974(w); 941(w); 906(w); 856(w); 841(w); 756(m); 737(m); 667(m). The intensities of the absorption bands are indicated as follows: (w)=weak, (m)=medium, and (st)= strong intensity. The characteristic absorption bands of the ATR-IR spectroscopy for the polymorphic form $B_{3,Ca}$ of the trihydrate of the calcium salt of valsartan are shown by the following values expressed in reciprocal wave numbers (cm^{-1}): 3594(w); 2959(w); 1621(st); 1577(m); 1458(m); 1405(m); 1354(w); 1273(w); 1012(w); 756(m); 737(m); 667(m). The error margin for all absorption bands of ATR-IR is ±2cm^{-1}.

Additionally, a new substance has been found as the monohydrate of the calcium salt of valsartan $C_{1,Ca}$. The bound water content is 3.1±0.3% measured with a thermobalance TGS-2 (Perkin-Emer Corp., Norwalk, Conn., USA). The total formula was calculated from the bound water content for the monohydrate $C_{1,Ca}$ as $(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}\cdot(0.8\pm0.2)H_2O$.

The solid state characterization of the monohydrate of the calcium salt of valsartan $C_{1,Ca}$ was executed by X-ray powder patterns with the evaluation of the interlattice plane intervals. The instrument used was a temperature-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL, equipped with a low and medium temperature attachement from Anton Paar GmbH, A-8054 Graz, Austria.

The characterization of the monohydrate of the calcium salt of valsartan $C_{1,Ca}$ with the interlattice plane intervals d is as such, whereby, in the following values are indicated with the appropriated error limits. The intensities of the d-values are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 16.0±0.3(m), 15.0±0.3(vst), 11.6±0.2(w), 9.9±0.2(vw), 9.4±0.2(vw), 8.02±0.1(vw), 7.53±0.1(vw), 7.02±0.1(vw), 6.47±0.05(vw), 6.11±0.0.5 (vw), 4.50±0.05(vw), 4.34±0.05(vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 16.0±0.3, 15.0±0.3, 11.6±0.2, 9.4±0.2, 7.53±0.1, 6.11±0.05.

Surprisingly, another new substance has been found, assigned with $D_{1,Ca}$ beeing the di-(calcium salt of valsartan) pentahydrate. The melting point of this new substance $D_{1,Ca}$ is T_{fus}=210±1.5° C. measured in a closed sample cell with a heating rate of 10K·min^{-1} and with a DSC called Pyris 1

from Perkin-Elmer Corp., Norwalk, Conn., USA. With the same instrument and the same procedures as above explained, the heat of fusion was determined. The heat of fusion is for the di-(calcium salt of valsartan) pentahydrate is approximated with 75 kJ.Mol^{-1}. The water content of the di-(calcium salt of valsartan) as pentahydrate was measured with a thermobalance TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA) and gave the value at the plateau of 225° C. of 8.1±0.5%. The total formula was elucidated from this bound water content for the substance $D_{1,Ca}$ as $[(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+}]_2 \cdot (4.7\pm0.3)H_2O$.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the di-(calcium salt of valsartan) pentahydrate $D_{1,Ca}$ as a function of temperature, was measured at a heating rate of 10 K·min^{-1}. The results for the di-(calcium salt of valsartan) pentahydrate are illustrated in table 6.

TABLE 6

Temperature [° C.]	Weight loss or water loss in %
25	0.1 ± 0.1
50	1.2 ± 0.2
75	2.4 ± 0.4
100	4.8 ± 0.4
125	7.1 ± 0.4
150	7.8 ± 0.4
175	8.0 ± 0.5
200	8.0 ± 0.5
225	8.1 ± 0.5
250	8.3 ± 0.5
275	8.6 ± 0.5

The solid state characterization of the di-(calcium salt of valsartan) pentahydrate $D_{1,Ca}$ was achieved with a Guinier camera (FR 522 from Enraf Nonius, Delft, NL) on an X-ray film in transmission geometry, using Cu—Ka_1 radiation at room temperature. Evaluations of the films for calculation of the interlattice plane intervals are made by a line-scanner (Johansson, Täby, S), and the reflection intensities are determined simultaneously. The reflections in the X-ray diffraction diagram could be evaluated to the following interlattice plane intervals d, whereby values are indicated with appropriate error limits. The intensities of the d-values are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak =w; and very weak=vw. d in [Å]: 15.5±0.3(vst), 11.5±0.2(st), 9.4±0.2 (vw), 9.04±0.1(w), 7.75±0.1(vw), 6.46±0.05(vw), 6.09±0.05(w), 5.82±0.05(vw), 5.66±0.05(vw), 5.16±0.05 (vw), 4.76±0.05(vw), 4.48±0.05(vw), 3.83±0.05(vw), 3.60±0.05(vw), 3.36±0.05(vw). The characteristic reflections in the X-ray diffraction diagram show the following interlattice plane intervals: d in [Å]: 15.5±0.3, 11.5±0.2, 9.4±0.2, 9.04±0.1, 6.46±0.05, 6.09±0.05, 5.82±0.05, 5.16±0.05, 4.48±0.05, 3.60±0.05.

Another new-type of crystalline, partially amorphous solids are falling into the groups of the magnesium salt hydrate and anhydrate of valsartan. In particular, the hexahydrate of the magnesium salt of valsartan in form of the polymorphic substance $A_{1,Mg}$ is a preferred substance. The specific optical rotation of hexahydrates of the magnesium salt of valsartan in water measured with a 1% solution at 20° C. is independent of the polymorphic form present as long as it is a hexahydrate $[\alpha]^D_{20}$=−38°. The thermal behaviour of this salt hydrate in the region of the melting point only reveals a certain chemical and physical instability. The thermal data are thus dependent on the measurement conditions. The instrument used for the calorimetric data is throughout a DSC Pyris 1 (Differential Scanning Calorimeter) obtained from Perkin-Elmer Corp., Norwalk, Conn. USA. The measurements are performed with samples enclosed in a sealed gold specimen container with an internal free volume of ca. 22 microliters, with a sample weight of 2 to 4 mg and with a heating rate of T_r=10K·min^{-1}. The melting point of hexahydrate of the magnesium salt of valsartan in the polymorphic form $A_{1,Mg}$ is 131±2° C. and the enthalpy of fusion is 47±3 kJ.Mol^{-1}. The hexahydrate of the magnesium salt of valsartan as the polymorphic form $A_{1,Mg}$ reveals the following loss of water as a function of temperature in using the method of thermogravimetry. The instrument used was a TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA) and the measurement was performed in a water free atmosphere. The heating rate selected was 10 K·min^{-1}. The weight loss is illustrated in table 7.

TABLE 7

Temperature [° C.]	Weight loss or water loss in %
25	0.1 ± 0.1
50	1.0 ± 0.2
75	6.1 ± 0.5
100	13.1 ± 0.5
125	15.8 ± 0.4
150	16.6 ± 0.4
175	17.2 ± 0.4
200	17.4 ± 0.4
225	17.6 ± 0.5
250	17.9 ± 0.5
275	18.6 ± 0.5

The theoretical water content is for the hexahydrate of the magnesium salt of valsartan 19.1%. The hexahydrate of the magnesium salt of valsartan in form of the polymorph $A_{1,Mg}$ has a bound water content at 225° C. determined as a weight loss of 17.6±0.5%. The total formula is calculated from this as $(C_{24}H_{27}N_5O_3)^{2-}Mg^{2+}\cdot(5.5\pm0.2)H_2O$.

The solid-state characterization of the magnesium salt of valsartan for the polymorphic form of the hexahydrate $A_{1,Mg}$ is achieved by a X-ray powder pattern and by the evaluation of the reflections into the interlattice plane intervals. The measurements have been made with three different X-ray instruments. The first instrument used is a Guinier camera (FR 522 from Enraf Nonius, Delft, NL) on an X-ray film in transmission geometry, with a Cu—Ka_1 radiation at room temperature. Evaluations of the films for calculation of the interlattice plane intervals are performed with a scanner from Johansson, Täby, S and the reflections intensities are determined simultaneously. The second instrument used for X-ray measurements of the new substance new substance $A_{1,Mg}$ is a temperatur-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL equipped with a low and medium temperature attachement from Anton Paar GmbH, A-8054 Graz. The third instrument applied in the solid state characterization is the powder diffractometer PW1710 from Philips Analytical X-ray. 7602 Almelo, NL. The characterization of the polymorph $A_{1,Mg}$ of the hexahydrate of the magnesium salt of valsartan is achieved from the interlattice plane intervals d of the ascertained X-ray measurements. In the following d values are listed with the appropriate error limits. The intensities are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]:19.6±0.3(vst), 16.6±0.3(vw), 10.3±0.2 (vw), 9.8±0.2(m), 7.3±0.1(w), 6.9±0.1(vw), 6.01±0.05(w), 5.92±0.05(w), 5.55±0.05(vw), 5.38±0.05(vw), 5.24±0.05 (vw), 5.15±0.05(vw), 5.06±0.05(vw), 4.90±0.05(m),

4.54±0.05(vw), 4.22±0.05(vw), 4.13±0.05(vw), 4.07±0.05 (w), 3.96±0.05(vw), 3.73±0.05(vw), 3.64±0.05(vw), 3.43±0.05(w), 3.29±0.05(vw), 3.22±0.05(vw), 3.11±0.05 (vw). The characteristic reflections in the X-ray diffraction diagram reveal the following plane intervals: d in [Å]: 19.6±0.3, 16.6±0.3, 10.3±0.2, 9.8±0.2, 7.3±0.1, 6.01±0.05, 5.92±0.05, 5.55±0.05, 5.38±0.05. 4.90±0.05, 4.13±0.05, 4.07±0.05, 3.43±0.05.

The substance in form of the tetrahydrate $B_{1,Mg}$ is a partially amorphous solid of the magnesium salt of valsartan. The tetrahydrate $B_{1,Mg}$ shows the following loss of water as a function of temperature measured with a thermobalance TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The heating rate selected was $10K \cdot min^{-1}$. The weight loss is tabulated in table 8.

TABLE 8

Temperature [° C.]	Weight loss or water loss in %
25	0 ± 0.1
50	2.1 ± 0.3
75	6.4 ± 0.5
100	9.5 ± 0.5
125	11.1 ± 0.4
150	12.0 ± 0.4
175	12.5 ± 0.4
200	12.8 ± 0.4
225	13.0 ± 0.4
250	13.6 ± 0.4
275	14.3 ± 0.4

The magnesium salt of valsartan in the polymorphic form of the tetrahydrate $B_{1,Mg}$ is showing a bound water content at 225° C. of 13.0±0.4%, and as shown for 25° C. in Table 8 practically no additional free water is present in the substance $B_{1,Mg}$. The measurements were performed with a thermobalance TGS-2 of the Perkin-Elmer Corp., Conn. USA. The total formula is therefore calculated as $(C_{24}H_{27}N_5O_3)^{2-}Mg^{2+}\cdot(3.8\pm0.2)H_2O$.

The solid-state characterization of the tetrahydrate of the magnesium salt of valsartan $B_{1,Mg}$ has been performed with an X-ray instrument by a so-called temperature-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL, equipped with a low and medium temperature attachement from Anton Paar GmbH, A-8054 Graz. Additional X-ray measurements were performed with a powder diffractometer PW 1710 from Philips Analytical X-ray, 7602 Almelo, NL. The crystalline parts of the substance $B_{1,Mg}$ are characterized in the solid state with the interlattice plane intervals d, which are given with appropriate error limits. The intensities are reported in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 15.8±0.3(vst), 11.0±0.2(w), 8.0±0.2(vw).

The new substance $C_{1,Mg}$ is a the trihydrate of the magnesium salt of valsartan. The water content was measured with a thermobalance TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The water content for this substance, namely the trihydrate of the magnesium salt of valsartan $C_{1,Mg}$ is 10.0±0.4%. The total formula is calculated from this $(C_{24}H_{27}N_5O_3)^{2-}Mg^{2+}\cdot(2.8\pm0.2)H_2O$.

The solid-state characterization of the trihydrate of the magnesium salt of valsartan $C_{1,Mg}$ has been performed with X-ray measurements by use of the temperature-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL equipped with a low and medium-temperature attachement from Anton Paar GmbH, A-8054 Graz. The characterization of the substance $C_{1,Mg}$ of the magnesium salt of the valsartan trihydrate is given with the interlattice plane intervals d obtained with X-ray measurements. In the following, d values are listed with the appropriate error limits. The intensities are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 17.9±0.3 (m), 10.2±0.2(w), 8.96±0.2(m), 7.18±0.1(w), 6.97±0.1(vw), 6.81±0.1(vw), 6.24±0.05(vw), 5.93±0.05(w), 5.84±0.05(w), 5.72±0.05(vw), 5.59±0.05(vw), 5.42±0.05(m), 5.25±0.05 (vw), 5.11±0.05(m), 5.01±0.05(st), 4.82±0.05(w), 4.67±0.05(w), 4.57±0.05(vw), 4.49±0.05(vw), 4.30±0.05 (m), 4.19±0.05(vst), 4.13±0.05(vst), 4.02±0.05(vst), 3.88±0.05(vw). The characteristic reflections in the X-ray diffraction diagram reveal the following plane intervals: d in [Å]: 17.9±0.3, 10.2±0.2, 8.96±0.2, 7.18±0.1, 5.93±0.05, 5.84±0.05, 5.42±0.05, 5.11±0.05, 5.01±0.05, 4.82±0.05, 4.67±0.05, 4.30±0.05, 4.19±0.05, 4.13±0.05, 4.02±0.05.

The magnesium salt of valsartan is also forming a substance as a monohydrate which is indicated with $D_{1,Mg}$. The water content was measured with a thermobalance TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The water content for the monohydrate $D_{1,Mg}$ is 2.8±0.3%. The total formula was calculated from this value with $(C_{24}H_{27}N_5O_3)^{2-}Mg^{2+}\cdot(0.74\pm0.2)H_2O$.

The solid-state characterization of the monohydrate of the magnesium salt of valsartan $D_{1,Mg}$ was achieved with X-ray measurements by use of the temperature-humidity powder diffraction chamber X'Pert from Philips Analytical X-ray, 7602 Almelo, NL. This X-ray instrument is equipped with a low and medium temperature attachement from Anton Paar GmbH, A-8054 Graz. The characterization of the new substance, namely the monohydrate of the magnesium salt of valsartan $D_{1,Mg}$ is demonstrated with the interlattice plane intervals d of the X-ray investigations. In the following d values are listed with the appropriate error limits. The intensities are given in brackets with the following abbreviations: very strong=vst; strong=st; medium=m; weak=w; and very weak=vw. d in [Å]: 15.1±0.2(st), 10.9±0.2(w), 10.3±0.2(vw), 7.66±0.1(vw), 7.21±0.1(vw), 5.12±0.05(vw), 4.75±0.05(vw). The characteristic reflections in the X-ray diffraction diagram for the monohydrate of the magnesium salt of valsartan reveal the following plane intervals: d in [Å]: 15.1±0.2, 10.9±0.2, 10.3±0.2, 7.66±0.1, 5.12±0.05.

Surprisingly, the crystalline salts of valsartan can be transformed into amorphous or partially amorphous substances. Crystalline and amorphous froms of corresponding chemical entities reveal different physico-chemical properties, related to the different structures of the crystalline and the amorphous form on a molecular level. The main difference is in the threedimensional organization of the solid particals. The crystalline particals or crystals reveal a short distance arrangement of a given number of molecules in well defined crystal lattice positions around each single molecule. All these first neighboring molecules of the set of molecules within an elementry cell of a crystal are within the whole crystal lattice in the same geometrical arrangement. The short distance arrangement of any single molecule is in crystal combined with the low range arrangement. In contrary, an amorphous substances reveals only a short range order for each molecule, however, the long range order is not existing within the amorphous solid particles. A consequence of this structural facts is the completely different behaviour of crystals or of an amorphous substance in heating up, starting at a low temperature within the the solid phases. Any crystalline substance is characterized with a melting point, which might be different for different poly-

morphs of the same chemical entity, however, together with the enthalpy of fusion the interrelation to the crystalline phase present is proofed. In contrary, an amorphous substance is never revealing a melting point and a enthalpy of fusion. But, in heating up, starting at a low temperature, an amorphous substance corresponds with a glass transition temperature, a temperature for which the molar heat capacity changes over a certain temperature interval. The broadness of this effect is depending on quite different qualities. The enthalpy change in heating up is for a glass transition always a uptake of energy by the sample. The crystalline and amorphous substances are discriminated at room temperature by several spectroscopical methods such as X-ray, Raman, IR. Additionally, a characterization at elevated temperature over the stability region of crystalline substances in the solid phase is also possible with a temperature-humidity powder diffraction chamber. A preferred characterization are the X-ray methods, because the amorphous substances reveal only a broad reflection, however, the crystalline substances are characterized with a discrete set of interlattice plane intervals.

The solid state characterization of the amorphous entity of the calcium salt hydrate of valsartan $E_{1,Ca}$ is performed with a DSC (Differential Scanning calorimeter) Pyris 1 from Perkin-Elmer Corp., Norwalk, Conn. USA. The same procedure must be executed as for the crystalline salts of calcium valsartan, namely because of existing salt hydrates, with a bound water content up to 13.2%, the measurements must be made in gold containers with a small internal free volume. In the present case, the gold containers had an internal free volume of ca. 22 microliters. Additional water, so-called free water could be present in the amorphous substance, detectable by a thermobalance as well as by the enthalpy of fusion for bulk water at 0° C. In an open sample pan or with a sample pan with a large internal free volume compared with the sample mass and depending on the water of the substance under investigation, the water evaporates partially or completely in transferring the chemical entity present partially or completely into the corresponding anhydrate or into a hydrate with a lower water content. Gold containers with a wall thickness 0.2 mm were used; after weighing the samples between 1.5 and 6 mg salt hydrate, they were sealed by cold welding. The amorphous substance of the calcium salt of valsartan $E_{1,Ca}$ related to the tetrahydrates and the trihydrates has a water content of 11±2%. The water content is measured using thermogravimetry, in a water-free N_2 atmosphere with a TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The glass transition was measured with sample weights of 3–5 mg in sealed gold containers with a internal free volume of ca. 22 microliters and applying a heating rate of 10 $K \cdot min^{-1}$. The glass transition temperature is determined for the amorphous calcium salt of valsartan $E_{1,Ca}$ as T_g=94±20° C. and the change of the specific heat capacity is at the glass transition temperature as Δc_p=0.6±0.2 $J \cdot g^{-1} \cdot K^{-1}$. No melting point and no enthalpy of fusion could be observed.

The amorphous substance of the calcium salt of valsartan $F_{1,Ca}$ related to the anhydrate has a water content of 9±2%. The water content is measured using thermogravimetry, in a water-free N_2 atmosphere with a TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The glass transition was measured with sample weights of 2–4 mg in sealed gold containers with a internal free volume of ca. 22 microliters and applying a heating rate of 10 $K \cdot min^{-1}$. The glass transition temperature is determined for the amorphous salt of valsartan $F_{1,Ca}$ as T_g=143±20° C. and the change of the specific heat capacity is at the glass transition temperature Δc_p=0.4±0.15 $J \cdot g^{-1} \cdot K^{-1}$. No melting point and no enthalpy of fusion could be observed. These combined thermodynamic data, melting point and enthalpy of fusion are an absolute prerequisite of a crystalline material or substance.

The amorphous substance of the magnesium salt of valsartan $E_{1,Mg}$ has a water content of 16±3%. The water content is less defined in an amorphous form, as the water molecules in an amorphous substance are weaker bound within the solid structure compared to a crystalline substance forming a hydrate. The water content is measured using thermogravimetry, in a water-free N_2 atmosphere with a TGS-2 (Perkin-Elmer Corp., Norwalk, Conn. USA). The glass transition was measured with sample weights of 2–4 mg in sealed gold containers with an internal free volume of ca. 22 microliters and applying a heating rate of 10 $K \cdot min^{-1}$. The glass transition temperature is T_g=78±20° C. and the change of the specific heat capacity is at the glass transition temperature Δc_p=0.5±0.25 $J \cdot g^{-1} \cdot K^{-1}$. No melting point and no enthalpy of fusion could be observed.

Preferred are polymorphic forms that are essentially free of amorphous forms.

A further object of the invention is the preparation of the salts according to the invention.

The salts or salt hydrates according to the invention, including amorphous or crystalline forms thereof, may be prepared as follows:

To form the salt, the process is carried out in a solvent system, in which the two reactants, namely the acid valsartan and the respective base, are sufficiently soluble. It is expedient to use a solvent or solvent mixture, in which the resulting salt is only slightly soluble or not soluble at all, in order to achieve crystallisation or precipitation. One variant for the salt according to the invention would be to use a solvent in which this salt is very soluble, and to subsequently add an anti-solvent to this solution that is a solvent in which the resulting salt has only poor solubility. A further variant for salt crystallisation consists in concentrating the salt solution, for example by heating, if necessary under reduced pressure, in slowly evaporating the solvent, e.g. at room temperature or at a temperature below room temperature, or by seeding with the addition of seeding crystals, or by setting up water activity required for hydrate formation and/or by seeding with the addition of the corresponding seeding crystals. Combinations of these production steps may be appropriately selected.

The solvents that may be used are for example C_1–C_5-alkanols, preferably ethanol and isopropanol, as well as C_1–C_5-dialkylketones, preferably acetone and mixtures thereof with water.

The antisolvents for salt crystallisation may be for example C_3–C_7-alkylnitriles, especially acetonitrile, esters, especially C_2–C_7-alkanecarboxylic acid-C_1–C_5-alkylester, such as ethyl or isopropyl acetate, di-(C_1–C_5-alkyl)-ethers, such as tert.-butylmethylether, furthermore tetrahydrofuran, and C_5–C_8-alkanes, especially pentane, hexane or heptane.

The dissolving and crystallising process is characterised in that

(i) valsartan and the appropriate base are brought to a reaction in a preferably water-containing, organic solvent,

(ii) the solvent system is concentrated, for example by heating, if necessary under reduced pressure and by seeding with seeding crystals or by slowly evaporating, e.g. at room temperature or at elevated temperatures, then crystallisation or precipitation is initiated and

(iii) the salt or salt hydrate obtained is isolated.

In the dissolving and crystallising process, the water-containing, organic solvent system employed is advanta-

geously a mixtures of alcohols, such as ethanol, and water, or alkyl-nitrile, especially acetonitrile, and water.

The equilibrating crystallisation process for producing hydrates is characterised in that

(i) valsartan and the appropriate base are added to a water-containing organic solvent,

(ii) the solvent is concentrated, for example by heating, if necessary under reduced pressure or by slowly evaporating, e.g. at room temperature

(iii) the residue of evaporation is equilibrated with the required amount of water by

(a) suspending the residue of evaporation, which is advantageously still warm, and which still contains some water, in an appropriate solvent or

(b) by equilibrating the water excess in the solvent at a given temperature, or with cooling from a given elevated temperature to a lower one; whereby in a) and b) the existing or added water is present in a quantity in which the water dissolves in the organic solvent and does not form an additional phase; and

(iv) the salt obtained is isolated.

The solvent system used as the water-containing organic solvent advantageously comprises mixtures of suitable alcohols, such as C_1–C_7-alkanols, especially ethanol, and water.

An appropriate solvent for equilibration is, for example, an ester such as C_1–C_7-alkane-carboxylic acid-C_1–C_7-alkylester, especially ethyl acetate, or a ketone such as di-C_1–C_5-alkylketone, especially acetone.

The equilibration process is notable for example for its high yields and outstanding reproducibility.

Especially, the alkaline earth metal salts of the present invention may be obtained in crystalline form as explained above and are in the form of hydrates, or mixtures of hydrates, or mixtures of hydrates with amorphous forms, from appropriate solvents that are conventionally used in production processes, such as esters, e.g. C_1–C_7-alkanecarboxylic acid-C_1–C_7-alkylesters, especially ethyl acetate, ketones, e.g. di-C_1–C_5-alkylketones, especially acetone, C_3–C_7-alkylnitriles, especially acetonitrile, or ethers, e.g. di-(C_1–C_5-alkyl)-ethers, such as tert.-butylmethylether, also tetrahydrofuran, or mixtures of solvents. By using the dissolving and crystallising process, or the water-equilibrating crystallisation process, the defined hydrates, which are present in crystalline and in polymorphous forms, may be obtained reproducibly.

The processes for forming salts are likewise objects of the present invention.

These salts or salt hydrates according to the invention are obtained for example by neutralising the acid valsartan with a base corresponding to the respective cation. This neutralisation is suitably effected in an aqueous medium, e.g. in water or a mixture of water and a solvent in which valsartan is more soluble than in water. Salts with weaker bases may be converted into other salts either by treating with stronger bases or by treating with acids and then neutralising with other bases.

Crystallisation, especially of the alkaline earth salt hydrates, is effected in water or an aqueous medium, which consists of water and at least one solvent that is miscible or partially miscible with water, i.e. not too non-polar, e.g. an alkanol such as methanol, ethanol, propanol, isopropanol, butanol, acetone, methyl ethyl ketone, acetonitrile, DMF, DMSO. The alkanol portion amounts to about 10% to 99%, or 20% to 90%, advantageously 30% to 70% by volume. For higher alkanols, the less polar solvent may also be present in lower concentrations. Owing to the restricted water-solubility of valsartan, the process frequently takes place in suspensions, or if valsartan is soluble in the other solvent component, in a solution.

In one embodiment, for example to produce the calcium salt of valsartan, an aqueous solution of valsartan is neutralised with a calcium hydroxide solution at room temperature and the solution is left to crystallise. In a preferred procedure, crystallisation is effected from a solvent mixture of water/ethanol, the ethanol proportion amounting to ca. 30% to 50% by volume. In an especially preferred form, crystallisation is effected in a closed system by transporting through a low temperature gradient (especially 1–2° C. at 40° C.) in 30% by volume of ethanol.

In a preferred variant, crystallisation may be optimised, e.g. accelerated, by adding at least one seed crystal.

To produce a salt of valsartan in a desired form as a hydrate, or an anhydrate and in a specific polymorph, or in a specific amorphous form thereof, a dissolving, chemical reaction, and crystallising process is used in particular, or a water-equilibrating crystallization, or an additional drying-equilibrating process. In the following, the processes consecutive to the dissolving and the chemical reaction shall be outlined:

(i) Transferring the obtained salthydrate, with a given molecular ratio water to salt of valsartan or with a mixture of hydrates, having different molecular ratios of water to salt of valsartan, or as a mixture of hydrates and the anhydrate of the given salt of valsartan, and all these entities and mixtures of entities in a specific polymorphic form, or in a specific amorphous form, or as mixtures of different polymorphs and different amorphous forms with or without a separation from the mother liquid into another liquid phase in which a considerable amount of the solid phase will not be dissolved, however, is present as a suspension. The liquid phase of this suspension is changed stepwise or continously in appropriate conditions such as temperature, pressure, volume, composition in respect to water, solvents, antisolvents in such a way that the salthydrate of choice is generated by a recrystallization process. The recrystallization can be forced by adding at least one seeding crystal.

(ii) Separate the obtained salthydrate in the crystalline state from the mother liquid, or from the liquid phase in which the salthydrate is suspended and transfer the wet cake with or without washing into a drier. The drier preferably used is a moving product drier, such as an example a paddle drier. The conditions in the drier and for the drying process have to be appropriate selected to obtain the salthydrate in the form to be produced.

In a preferred embodiment of the present invention, the different hydrates and polymorphic and amorphic forms thereof can be prepared by using the thermobalance procedure as follows: Starting from e.g. the $A_{0,Ca}$ or the $A_{0,Mg}$ form, respectively, said forms are (i) dehydrated, e.g. totally or partially, for example, in a thermobalance apparatus e.g. TGS-2, or in a temperature-humidity powder diffraction chamber, e.g. X'Pert, or in Differential Scanning Calorimeter, e.g. DSC Pyris 1; then (ii) equilibrated by exposure to different relative air humidities over different periods of time, optionally (iii) relaxed over different periods of time, and then, if necessarey, (iv) isolated.

The dehydration step is carried out essentially by dehydrating the corresponding starting material in a water free atmosphere, under inert gas, in a defined temperature range and over a defined time intervals. A suitable temperature is

from room temperature to 100° C. Suitable time intervals are from 30 minutes to 70 hours.

The equilibration step is carried out by exposing the dehydrated form to different air humidities. Preferred air humidities range from 20% to 70% relative air humidity.

The relaxation period is between 30 minutes to 50 hours. The preferred temperature range for the equilibration step is between 20° C. and 25° C.

The form according to the present invention is preferably isolated by crystallisation.

Important conditions among others are the relative humidity of the atmosphere in the drier, the temperature of the atmosphere and the temperature of the dry product, all these parameters as a function of the drying degree and also the drying time interval which also defines the final state of the equilibrated product. The main driving force for a hydrate formation of a salthydrate of valsartan during the crystallization or precipitation process, or during a recrystallization process as a suspension or as a product in a drying process is the activity of the water in the liquid phase or the partial pressure of the water in the atmosphere of a drier. The composition of the liquid phase in which the salthydrate of valsartan is suspended and its temperature are decisive for the activity of the water. In the drier, the partial pressure of the water is adjusted under equilibrium or non-equilibrium conditions with conditions such as relative humidity of the inlet gas stream, the temperature of the drier and the temperature of the substance dried, the uptake of water or the dehydration of the substance dried, the flow rate of the atmosphere and the mass of the substance dried. Of course, also the ratio of the water molecules to the salt molecules at the beginning and the end of the drying process and the kinetic of the dehydration or hydration are factors influencing the partial pressure of the water in the drier.

An additional thermodynamic parameter, which is decisive for the salt hydrate of valsartan and the polymorphic form of the final state of the product, is the temperature. The thermodynamic stability regions of the salthydrates of valsartan are depending also on temperature, or in other words certain salthydrates of valsartan and polymorphs thereof are only stable for given temperature regions. As an example, a selected salthydrate of valsartan can only be crystallized or can only be recrystallized also from a solution if the temperature is selected properly.

The salts according to the invention may be used e.g. in the form of pharmaceutical preparations, which contain the active substance e.g. in a therapeutically effective amount of the active substance, optionally together with a pharmaceutically acceptable carrier, for example with an inorganic or organic, solid or optionally also liquid pharmaceutically acceptable carrier, which is suitable for enteral, e.g. oral, or parenteral administration.

The invention relates in particular to a pharmaceutical composition, especially in a solid dosage unit, preferably for oral administration, optionally together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations of this kind may be used for example for the prophylaxis and treatment of diseases or conditions which may be inhibited by blocking the AT_1 receptor for example a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, and

(e) glaucoma.

Primary usages are for the treatment of high blood pressure and congestive heart failure, as well as post-myocardial infarction.

The person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the salts of the present invention or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardovasc. Pharmacol. 27:347–354, 1996.

For example, the valuable potential of the salts or combinations of the present invention for the prevention and treatment of myocardial infarction can be found using the following test model.

Study Design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 5 treatment groups characterized by following features:

sham-operated animals

CAO+vehicle

CAO+a salt according to the present invention, optionally

CAO+a salt according to the present invention+a combination partner.

During the study following variables are measured:

infarct size

LV chamber volume

interstitial and perivascular collagen density in spared LV myocardium

COL-I and COL-III protein content in spared LV myocardium by Western blot

cardiomyocytes cross-sectional area and length in sections of LV myocardium

plasma concentrations of renin and aldosterone

urine concentration of sodium, potassium and aldosterone

blood pressure in conscious animals

LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct Size

Six μm-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system

(Carl Zeiss Vision) using a software specifically developed (Porzio et al., 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio et al., 1995).

Histology

Hearts are fixed in situ, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson et al., 1998).

Collagen Content in LV Spared Myocardium

LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for colagen type I) or peroxidase (collagen type III).

Left Ventricular Chamber Volume

LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length.

The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic et al., 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left Ventricular Hemodynamics

A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time (+dP/dt) and heart rate.

Non-invasive Blood Pressure

Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine Electrolytes, Hormones

Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C_{18} columns (Varian), separated by HPLC (Apex-II C18, 3 μm, 50×4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein et al., 1981). Plasma and urine aldosterone, and plasma angiotensin II is determined with specific radioimmunoassays (Aldoctk-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flamme photometry.

Sample Size

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial disfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGFb, PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelian dysfunction can be demonstrated in the following pharmacological test:

Material and Methods

Male 20–24 week-old SHR, purchased from RCC Ldt (F üllingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1–2.7).

The rats can be divided into 2 or 3 groups: group 1, control (n=e.g. 40); Group 2, a salt according to the present invention; n=e.g. 40); for testing combinations Group 3, combination partner;(n=e.g. 30). The drugs are administered in drinking fluid. The pressure effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reduced after treatment with a salt according to the present invention (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na^+ and K^+ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5% EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical Analysis

All data are expressed as mean±SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, 7 for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

An improvement of regression of artherosclerosis without effecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414–419 (1999).

That the salts or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033–1037.

That the salts or combinations according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87–95 (1998).

The present pharmaceutical preparations which, if so desired, may contain further pharmacologically active substances, are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes, and contain from about 0.1% to 100%, especially from about 1% to about 50%, of lyophilisates up to 100% of the active substance.

The invention similarly relates to compositions containing the salts according to the invention.

The invention similarly relates to the use of the salts according to the invention preferably for the production of pharmaceutical preparations, especially for the prophylaxis and also for the treatment of diseases or conditions which may be inhibited by blocking the AT_1 receptor. Primary usages are for the treatment of high blood pressure and congestive heart failure, as well as post-myocardial infarction.

The invention similarly relates to the use for the prophylaxis and treatment of diseases or conditions which may be inhibited by blocking the AT_1 receptor, characterised in that a patient, including a human patient, requiring such treatment is administered with a therapeutically effective amount of a salt according to the invention, optionally in combination with at least one composition for the treatment of cardiovascular diseases and related conditions and diseases listed hereinbefore or hereinafter.

The invention similarly relates to combinations, e.g. pharmaceutical combinations, containing a salt of the present invention or in each case a pharmaceutically acceptable salt thereof in combination with at least one composition for the treatment of cardiovascular diseases and related conditions and diseases as listed hereinbefore or hereinafter, or in each case a pharmaceutically acceptable salt thereof. Combinations with other compositions for the treatment of cardiovascular diseases and related conditions and diseases as listed hereinbefore or hereinafter, or in each case a pharmaceutically acceptable salt thereof, are likewise objects of the present invention.

The combination may be made for example with the following compositions, selected from the group consisting of a:

(i) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(ii) angiotensin converting enzyme (ACE) Inhibitor or a pharmaceutically acceptable salt thereof,

(iii) calcium channel blocker or a pharmaceutically acceptable salt thereof,

(iv) aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(v) aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vi) dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(vii) endothelin antagonist or a pharmaceutically acceptable salt thereof,

(viii) renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ix) diuretic or a pharmaceutically acceptable salt thereof.

HMG-Co-A reductase inhibitors (also called β-hydroxy-β-methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol in blood.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred HMG-Co-A reductase inhibitors are those agents which have been marketed, most preferred is fluvastatin and pitavastatin or, in each case, a pharmaceutically acceptable salt thereof.

The interruption of the enzymatic degradation of angiotensin I to angiotensin II with so-called ACE-inhibitors (also called angiotensin converting enzyme inhibitors) is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

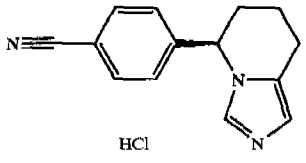
Aldosterone synthase inhibitor is an enzyme that converts corticosterone to aldosterone to by hydroxylating cortocosterone to form 18-OH-corticosterone and 18-OH-

corticosterone to aldosterone. The class of aldosterone synthase inhibitors is known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

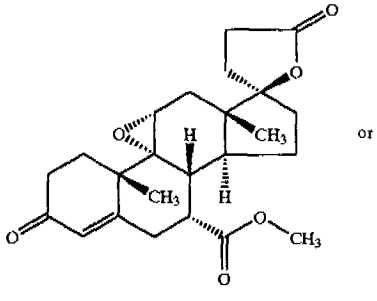
Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (U.S. Pat. Nos. 4,617,307 and 4,889,861) of formula



A preferred steroidal aldosterone antagonist is eplerenone of the formula

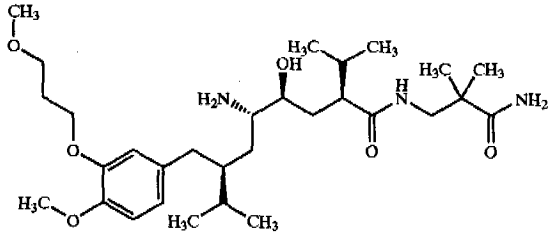


spironolactone

A preferred dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor is, for example, omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or, if appropriable, a pharmaceutically acceptable salt thereof.

A preferred endothelin antagonist is, for example, bosentan (cf. EP 526708 A), furthermore, tezosentan (cf. WO 96/19459), or in each case, a pharmaceutically acceptable salt thereof.

A renin inhibitor is, for example, a non-peptidic renin inhibitor such as the compound of formula



chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide. This representative is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

Dosaging may depend on various factors, such as mode of application, species, age and/or individual condition. For

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
RESPUESTA AL RECURSO DE REPOSICIÓN

2020
Bogotá D.C.,

Abogado
DILIA MARÍA RODRÍGUEZ D'ALEMAN

REFERENCIA:	Radicación No.	04 086836
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	
	Folios	05

TÍTULO "Sales de Valsartán"

En atención al Recurso de Reposición interpuesto, se hacen las siguientes aclaraciones:

Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 5 – 121, el nuevo capítulo reivindicatorio de los folios 294 – 296 y los argumentos del solicitante.

Objeto de la Invención

El problema planteado en esta solicitud es la necesidad de formas cristalinas de valsartán, más fáciles de manejar en los procedimientos de secado y de granulación después de la etapa final del procedimiento de la preparación química.

Para resolver este problema técnico la solicitud en estudio proporciona sales e hidratos de sal de valsartán que se selecciona del grupo de metales alcalinotérreos que consisten de la sal de magnesio y de la sal de calcio, así como mezclas de sal o respectivamente una forma amorfa, un solvato, en especial un hidrato, así como su forma polimorfa.

Respuesta a los Argumentos del Solicitante

En atención a los argumentos del solicitante se hacen las siguientes aclaraciones:

1. Dice el solicitante en el Folio 318: "la referencia escogida por el despacho en el examen de búsqueda, fue seleccionada partiendo del conocimiento de la invención en estudio, sin tener en cuenta cuál era el estado del arte en el momento de la fecha de prioridad reconocida de la solicitud en estudio, es decir antes del 4 de Febrero de 2002, pues si bien el documento **D1** que pertenece al mismo solicitante, fue publicado un mes antes de la fecha de prioridad de la presente solicitud, también es cierto que una persona

medianamente versada en la materia no estaba en la capacidad de encontrar en el término de un mes el problema técnico que se plantea en esta solicitud, que ha venido solucionando el solicitante desde hace tiempo atrás".

Se aclara al solicitante que se realizó revisión de las fechas de publicación y de prioridad, encontrándose que el documento WO/2002/06253 considerado como **D1;** posee un documento de prioridad de fecha de 19 de julio de 2000, el cual fue publicado el 24 de enero de 2002, mientras que la solicitud presentada en su documento de prioridad tiene una fecha de 04 de febrero de 2002, con una fecha de publicación de 03 de febrero de 2003. De acuerdo con lo anterior, es claro que desde el año 2000, ya se encontraba en estudio las sales de valsartán; y que dicho documento se publicó antes de la solicitud presentada cumpliendo con los requerimientos de la D486.

2. Afirma el solicitante en el Folio 319: "la evaluación de la altura inventiva partió del mismo conocimiento de la solicitud en estudio, sin apreciar si las nuevas formas obtenidas para las sales de valsartán, aquí reclamadas habrían sido obvias y susceptibles de derivación evidente a partir del documento **D1**"
   En el siguiente párrafo "el documento **D1** no le indica o sugiere a una persona medianamente versada en la materia la manera cómo se llegan a las sales de valsartán ahora reclamadas" y "el documento **D1** no anticipa cuáles serían las formas cristalinas que se podrían llegar a obtener en un futuro, simplemente porque no es posible predecir ni las condiciones en que un cristal se puede formar ni el cristal que se formará".

Se aclara al solicitante que aunque no se tiene certeza que los compuestos puedan cristalizar en una forma u otra, es claro que dicho proceso depende de la sustancia en cuanto a su propia naturaleza y de los solventes empleados. En la solicitud presentada, el objeto no fue el proceso de preparación de las sales sino de los cristales obtenidos. Estas sales ya se encontraban previamente divulgadas en **D1** y fueron caracterizados mediante ensayos rutinarios de difracción de rayos X, los cuales pueden ser desarrollados por una persona medianamente versada en el arte de acuerdo con las farmacopeas oficiales (Ver entre otras USP23), y por lo tanto sin emplear habilidad inventiva.

3. Argumenta en el Folio 320:" en el proceso de obtención de una nueva forma cristalina por primera vez no se sigue un procedimiento estándar similar a una receta y ya he mencionado que anteriormente para la obtención de esas condiciones que le favorezcan, se requieren de nuevos procedimientos" y en el Folio 321 "resulta errado pensar que porque en un documento se revelan sales cristalinas de un compuesto y se mencionen los solventes en los cuales se realizó un proceso de cristalización, se puede generalizar y estandarizar dicho proceso para volverlo protocolo rutinario para producir todas las otras formas cristalinas que se puedan obtener de un compuesto a posteriori"

Se aclara al solicitante que el objeto de la solicitud no fue el proceso de preparación sino las sales cristalinas y sus patrones de difracción de rayos X.

4. Sostiene el solicitante en el Folio 321:"la obtención de una nueva forma cristalina no se puede considerar como un acto rutinario, juega un papel importante la creatividad del investigador, es él quien tiene que establecer las mejores condiciones de esas variables para la obtención de esa nueva forma cristalina. Por lo tanto, para la obtención de las diferentes formas cristalinas se

requiere diferentes condiciones, las cuales son dadas o impuestas por el investigador"

Se le reitera nuevamente al solicitante que aunque no corresponde al objeto de la solicitud presentada, el proceso de cristalización; no se evidencia que haya habido creatividad en el investigador puesto que los compuestos ya se encontraban previamente divulgados y el investigador, el único procedimiento que realizó fue el de caracterizarlo por técnicas rutinarias para el experto en la materia como es el patrón de difracción de rayos X, para la determinación de la forma cristalina, careciendo por lo tanto de altura inventiva.

5. Reitera el solicitante en el Folio 321: "existen las suficientes pruebas de que las sales de la solicitud reclamadas en la presente invención tienen un alto grado de disociación en agua y por lo tanto una solubilidad en agua sustancialmente mejorada" y coloca en consideración la patente estadounidense de la solicitud presentada US 6,869,970. Además el solicitante en el Folio 322, refiere: "con dichas sales se puede obtener un mejor manejo en los procesos de secado y granulación".

Se aclara al solicitante (Ver Folio 9), que es claro que tanto las sales cristalinas, como las amorfas y los hidratos poseen las mismas ventajas en cuanto a su disociación en agua y por lo tanto la solubilidad en agua se encuentra sustancialmente mejorada, sin embargo no se evidencia en la solicitud presentada que estas propiedades a la luz del documento **D1** (Ver Folio 245, líneas 6-8), sean superiores e inesperadas. Además tampoco se evidencia en sus características farmacológicas, pues se presenta la misma actividad biológica de los compuestos de la solicitud presentada y los previamente divulgados en **D1**.

Conclusión

Teniendo en cuenta lo anterior, se recomienda ratificar la negación del privilegio solicitado para las reivindicaciones 1 – 12, folios 294 – 296.

Bogotá D.C.,

CONCEPTO TÉCNICO 0287	DIRECTORA DE NUEVAS CREACIONES	EXAMINADOR TÉCNICO 202070