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(54) Title: NEW PHARMACEUTICAL COMPOSITION CONTAINING CANDESARTAN CILEXETIL AS LIPOPHILIC CRYSTALLINE SUBSTANCE

(57) Abstract: New composition of candesartan cilexetil is prepared using up to 20% of carrageenan which suitably stabilized the active ingredient against degradation during the tableting.

NEW PHARMACEUTICAL COMPOSITION CONTAINING CANDESARTAN CILEXETIL AS LIPOPHILIC CRYSTALLINE SUBSTANCE

FIELD OF THE INVENTION

The present invention from the field of pharmaceutical industry relates to the pharmaceutical composition comprising pharmaceutically active lipophylic substances, which are susceptible to degradation while being formulated, that is during the process of incorporating aforesaid substance into a composition, particularly into a finished dosage form, preferably into tablets. In particular the invention relates to the pharmaceutical compositions comprising active lipophylic substance, which is candesartan cilexetil, and optionally another active pharmaceutical ingredient, and to processes for their preparation. Specifically the invention relates to the use of small amounts of carrageenan in the process for manufacturing of aforesaid pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Candesartan cilexetil is an example of a lipophylic substance used as an antihypertensive agent and its therapeutic uses were disclosed in US 5,196,444, which also disclosed a crystalline form of candesartan cilexetil. It is believed that crystals of candesartan cilexetil are deformed by the elevated pressure during the tableting, which causes degradation / decomposition of the active substance during processing and/or storage and/or at the elevated temperature, which may be manifested as lowering the content thereof or increase of amount of impurities or related substances. US 5,534,534 describes incorporation of an oily substance having a lower melting point into a formulation containing candesartan cilexetil. The melting point of said oily substance selected from hydrocarbons, higher fatty acids, higher alcohols, fatty acid esters of polyhydric alcohols, higher alcohol ethers of polyhydric alcohols and polymers or copolymers of alkylene oxide ranges from 20 to 90 ° C. Not wishing to be bound by the theory it is believed that the oily substance probably melts during the tableting as a result of the raised temperature caused by the friction between the particles and that this molten substance probably attenuates the friction between the crystals of candesartan cilexetil and/or between the crystals of candesartan cilexetil and other particles in the tableting mixture and consequently minimizes crystalline disorders of candesartan cilexetil crystals. The same approach could be used in manufacturing a pharmaceutical composition of antihypertensive agent in combination with diuretic such as manidipine hydrochloride or hydrochlorothiazide.

Present invention discloses new pharmaceutical compositions comprising active pharmaceutical ingredients, preferably a lipophylic substance, sensitive to pressure, such as candesartan cilexetil, and optionally another active pharmaceutical ingredient such as a diuretic and processes for their preparation.

DICLOSURE OF THE INVENTION

The invention is in a general aspect a solid pharmaceutical composition comprising a lipophilic active pharmaceutical ingredient optionally in combination with at least one another active pharmaceutical ingredients characterized in that it comprises from 2 to 20 % of a hydrophilic substance with hydrocolloidal properties.

Preferably the hydrophilic substance with hydrocolloidal properties is a polysaccharide extracted from algae, more preferably a carrageenan, in preferred amount around 10% to 1000% relative in weight to active, preferably in comparable amount, while the lipophilic active pharmaceutical ingredient is preferably candesartan cilexetil, and another optional active pharmaceutical ingredient is preferably hydrochlorotiazide or manidipine hydrochloride.

In a specific aspect the invention is a solid pharmaceutical composition comprising at least one lipophilic active pharmaceutical ingredient, which is preferably candesartan cilexetil, preferably in amount of up to 20% by weight and up to 20 % by weight of a carrageenan and from 40 to 80% by weight of one or more diluents and from 2 to 25% by weight of one or more disintegrants and up to 5% by weight of one or more binders.

Most specific aspect of the invention is solid pharmaceutical composition comprising candesartan cilexetil and optionally or hydrochlorothiazide and up to 20 %, preferably up to 10%, more preferably between 2% and 5% by weight of a carrageenan and from 40 to 80% by weight of one or more diluents and from 2 to 25% by weight of one or more disintegrants and up to 5% by weight of one or more binders, preferably where it comprises of from 1 to 20% by weight of candesartan cilexetil, from 1 to 20% by weight of carrageenan, from 40 to 80% by weight of one or more diluents, from 2% to 25% by weight of one or more disintegrants and from 0,5% to 5% by weight of one or more binders.

In an aspect, the composition would comprise from 1 to 20% by weight of candesartan cilexetil, optionally from 1% to 20% by weight of hydrochlorotiazide and from 1 to 20% by weight of carrageenan.

Composition described above may additionally comprise together from 40 to 80% by weight of lactose and starch, from 2% to 25% by weight of sodium carboxymethylcellulose and from 0,5% to 5% by weight of povidone.

Preferably the pharmaceutical composition which is an aspect of the invention will be in a form of a tablet, comprising between about 1% and about 10% by weight of an active ingredient, preferably candesartan cilexetil and between 2% and 20% of carrageenan. In more preferred aspect it will additionally to active ingredient and carrageenan comprise one or more inactive ingredients selected from group consisting of lactose, starch, povidone, carboxymethylcellulose sodium and magnesium stearate.

In yet another aspect the invention represents a use of a composition as described above for the manufacturing of a medicament.

Further aspects of the invention are the use of carrageenan in the manufacturing of a stable pharmaceutical composition, preferably comprising a lipophylic crystalline substance as an active pharmaceutical ingredient, more preferably comprising candesartan cilexetil.

In another aspect the invention is embodied in a process for preparing a stable pharmaceutical composition by tableting, by making first granulate comprising active pharmaceutical ingredient characterized in that the carrageenan is added to the granulate before tableting and preferably the main pressure used in tableting is at maximum 20 kN.

Specific steps in the process described above are:
a) providing a granulate comprising candesartan cilexetil;
b) mixing said granulate with one or more components where one of the components is carrageenan;
c) tableting the mixture obtained in previous step

A method of treating hypertension by administering a pharmaceutical composition comprising candesartan cilexetil and carrageenan to the patients in need thereof is also an aspect of the invention

DETAILED DESCRIPTION OF THE INVENTION

Stable formulations of an active pharmaceutical ingredient, such as described above have been developed by preparing pharmaceutical compositions comprising among excipients hydrophilic substances, preferably substances with hydrocolloidal properties which are conveniently selected from natural or synthetic polysaccharides with suitable properties, such as ability of swelling in an aqueous solvents which stabilize aforementioned active pharmaceutical ingredients against degradation or decomposition during the manufacturing of a pharmaceutical composition and/or during storage and/or at elevated temperatures. Prefered example of such stabilizing excipient is carrageenan, which is preferably added to the granulate in relatively small amounts before manufacturing of a finished solid dosage form. In a specific example carrageenan present in a pharmaceutical composition comprising candesartan cilexetil allows the application of low pressures during the tableting process without affecting the quality of the tablets. The pressures are selected to be low enough to prevent the crystalline disorders of candesartan cilexetil particles, such as beloow 20 kN, preferably below 10 kN, in certain embodiments preferably below 7 kN.

Substances, used within the scope of our invention, such as the carrageenans and agar possess hydrophilic properties (which means that they interact with water in a manner that they for example freely mix with it and/or swell in it and/or form a gel, absorpt it) and hydrocolloidal properties (meaning forming colloidal dispersion, and or forming colloidal gel when dispered in water) and preferably have m.p. above 90 ° C (e.g. no significant endothermic changes are observed on DSC thermogram for carrageenan upon heating to approximately 100 ° C). Carrageenans are natural polysaccharides extracted from algae. They consist of the sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked alpha-1,3 and beta-1,4 in the polymer. They may be dried and ground to required specifications. Typical carrageenans are for example sold under tradenames Gelcarin1 GP-379 NF, Gelcarin GP-812 NF, and Gelcarin GP-911 NF, Viscarin1 GP-109 NF, and Viscarin GP-209 NF by FMC Corp.

Solid pharmaceutical composition in accordance with our invention comprise active pharmaceutical ingredient in amount up to 80% , preferably up to 25% more preferably from 1 to 10% by weight optionally in combination with another active pharmaceutical ingredients in a pharmaceutically acceptable carrier which comprises a relatively low amount of up to 20%, preferably from 2 to 20%, preferably less than 10%, most preferably about 5% of a stabilizing hydrophilic substances, preferably substances with hydrocolloidal properties such as carrageenan or agar. The pharmaceutical carrier can suitably comprise other inactive ingredients, preferably from 10 to 80%, more preferably from 40 to 60% of one or more diluents or fillers, such as lactose monohydrate, from 2 to 25%, more preferably above 10% of one or more disintegrants, such as starch or carboxylmethylcellulose sodium, up to 5%, preferably up to 2,5% of one or more suitable binders, such as povidone, one or more glidants, pigments and any other commonly used excipients.

Optional other inactive ingredients (excipients) may function as different fillers, binders, disintegrants, glidants, lubricants and/or excipients that enhance the absorption of drugs from gastrointestinal tract. Fillers may be selected from microcrystalline cellulose, powdered cellulose, lactose, starch, pregelatinized starch, sucrose, glucose, mannitol, sorbitol, calcium phosphate, calcium hydrogen phosphate, aluminium silicate, sodium chloride, potassium chloride, calcium carbonate, calcium sulphate, dextrates, dextrin, maltodextrin, glycerol palmitostearate, hydrogenated vegetable oil, kaolin, magnesium carbonate, magnesium oxide, polymethacrylates, talc, and others. Preferred fillers are starch and lactose monhydrate. Suitable binders may be starch, pregelatinized starch, gelatine, sodium carboxymethylcellulose, polyvinylpyrrolidone, alginic acid, sodium alginate, acacia, carbomer, dextrin, ehylcellulose, guar gum, hydrogenated vegetable oil, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, glucose syrup, magnesium aluminium silicate, maltodextrin, polymethacrylates. Preferably starch and polyvinylpyrrolidone are used. Suitable disintegrants may be selected from starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, cross-linked sodium carboxymrethylcellulose, calcium carboxymethylcellulose, methylcellulose, microcrystalline cellulose, powdered cellulose, polacrilin potassium, cross-linked polivinylpyrrolidone, alginic acid, sodium alginate, colloidal silicon dioxide, guar gum, magnesium aluminium silicate, and others. Preferred disintegrant is sodium carboxymethylcellulose. Suitable glidants may be magnesium stearate, calcium stearate, aluminium stearate, stearic acid, palmitic acid, cetanol, stearol, polyethylene glycols of different molecular weights, magnesium trisilicate, calcium phosphate, colloidal silicon

dioxide, talc, powdered cellulose, starch and others.. Suitable lubricants may be selected from stearic acid, calcium, magnesium, zinc or aluminium stearate, siliconized talc, glycerol monostearate, glycerol palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, light mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, talc and others. Preferred lubricants is magnesium stearate. Suitable absorption enhancers may be selected from surface active agents, fatty acids, middle chain glycerides, steroide detergents (salts of bile salts), acyl carnitine and alcanoloil choline (esters of carnitine and choline and fatty acids with middle chain and long chain), N-acyl derivatrives of alpha-amino acids and N-acyl derivatives of non-alpha-amino acids, chitosanes and other mucoadhesive polymers.

This invention is in specific embodiment an orally administrable tablet comprising following amounts of candesartan cilexetil: 2, 4, 8, 16 or 32 mg.

The pharmaceutical compositions of our invention can be prepared as follows: In a granulator equipped with stirrer a powder mixture of one or more excipients such as diluents, disintegrants, binders is charged together with an active pharmaceutical ingredient. The mixture is granulated with a granulating liquid and to the granulating mixture or to the granules a stabilizing hydrophilic substances, preferably substances with hydrocolloidal properties is added optionally together with any other commonly used excipeints. Finaly the tablets are made by a gentle tableting process, that is the one where the main pressure is at maximum 20 kN, preferably 10 kN.

In specific embodiment of the invention a mixture of lactose with candesartan cilexetil, corn starch, povidone and pigment is granulated with water and dried in a fluid bad to give granules. To dried granules are added carrageenan, carboxymethylcellulose sodium and magnesium stearate. Tableting of thus obtained mixture is performed on a rotary tableting machine with 10 mm diameter flat–faced punches using the main pressure maximum 10 kN.

More specifically the present invention relates in an embodiment to a combination of two active ingredients, for example candesartan cilexetil as a angiotensin II antagonist with hydrochlorothiazide as a diuretic to achieve especially remarkable synergistic effects. The tablets are prepared as described above where the second active ingredient, alone or mixed with some other excipients is suitably added to the mixture to form granulate or to the already formed granulate. Hydrochlorothiazide presents 3 -10 w.w.% in the tablets.

Within the scope of invention are also the alternatives, such as direct compression of powders or preparation of pellets and their incorporation into a finished dosage form.

The present invention is exemplified in the following examples of pharmaceutical compositions comprising a lipophylic pharmaceutical active ingredient:

Example 1: Candesartan cilexetil 32 mg

Dose	**32 mg**	**%**
Candesartan cilexetil	32.00 mg	10.0
Lactose monohydrate	217.00 mg	67.8
Corn starch	40.00 mg	12.5
Ferric oxide yellow	0.40 mg	0.1
Povidone	9.60 mg	3.0
Carrageenan	12.00 mg	3.8
Carboxylmethylcellulose sodium	8.00 mg	2.5
Magnesium stearate	1.00 mg	0.3
Total	320.00 mg	100.0

Example 2: Candesartan cilexetil 16 mg

Dose	**16 mg**	**%**
Candesartan cilexetil	16.00 mg	10.0
Lactose monohydrate	108.50 mg	67.8
Corn starch	20.00 mg	12.5
Ferric oxide yellow	0.20 mg	0.1
Povidone	4.80 mg	3.0
Carrageenan	6.00 mg	3.8
Carboxylmethylcellulose sodium	4.00 mg	2.5
Magnesium stearate	0.50 mg	0.3
Total	160.00 mg	100.0

Example 3: Candesartan cilexetil 8 mg

Dose	8 mg	%
Candesartan cilexetil	8.00 mg	5.0
Lactose monohydrate	116,60 mg	72.9
Corn starch	20.00 mg	12.5
Ferric oxide yellow	0.10 mg	0.1
Povidone	4.80 mg	3.0
Carrageenan	6.00 mg	3.7
Carboxylmethylcellulose sodium	4.00 mg	2.5
Magnesium stearate	0.50 mg	0.3
Total	160.00 mg	100.0

Example 4: Candesartan cilexetil 4 mg

Dose	4 mg	%
Candesartan cilexetil	4.00 mg	2.5
Lactose monohydrate	120.70 mg	75.5
Corn starch	20.00 mg	12.5
Povidone	4.80 mg	3.0
Carrageenan	6.00 mg	3.7
Carboxylmethylcellulose sodium	4.00 mg	2.5
Magnesium stearate	0.50 mg	0.3
Total	160.00 mg	100.0

Example 5: Candesartan cilexetil 2 mg

Dose	2 mg	%
Candesartan cilexetil	2.00 mg	1.2
Lactose monohydrate	122.70 mg	76.8
Corn starch	20.00 mg	12.5
Povidone	4.80 mg	3.0
Carrageenan	6.00 mg	3.7
Carboxylmethylcellulose sodium	4.00 mg	2.5
Magnesium stearate	0.50 mg	0.3
Total	160.00 mg	100.0

Example 6: Candesartan cilexetil 32 mg

Dose	**32 mg**	**%**
Candesartan cilexetil	32.00 mg	8.0
Lactose monohydrate	279.25 mg	69.8
Corn starch	50.00 mg	12.5
Ferric oxide yellow	0.50 mg	0.1
Povidone	12.00 mg	3.0
Carrageenan	15.00 mg	3.8
Carboxylmethylcellulose sodium	10.00 mg	2.5
Magnesium stearate	1.25 mg	0.3
Total	400.00 mg	100.0

Tablets comprising besides a lipophylic pharmaceutical active ingredient such as candesartan cilexetil also another active ingredient, for example a diuretic such as manodipine or hydrochlorotiazide can be prepared as described in the following examples:

Example 7: Candesartan 8 mg/ Hydrochlorothiazide 12.5 mg

Dose	**8 mg**
Candesartan cilexetil	8.00 mg
Hydrochlorothiazide	12.50 mg
Lactose monohydrate	104.10mg
Corn starch	20.00 mg
Ferric oxide yellow	0.10 mg
Povidone	4.80 mg
Carrageenan	6.00 mg
Carboxylmethylcellulose sodium	4.00 mg
Magnesium stearate	0.50 mg
Total	160.00 mg

Example 8: Candesartan 16 mg/ Hydrochlorothiazide 12.5 mg

Dose	**16 mg**
Candesartan cilexetil	16.00 mg
Hydrochlorothiazide	12.50 mg
Lactose monohydrate	96.10 mg
Corn starch	20.00 mg
Ferric oxide yellow	0.10 mg
Povidone	4.80 mg
Carrageenan	6.00 mg
Carboxylmethylcellulose sodium	4.00 mg
Magnesium stearate	0.50 mg
Total	160.00 mg

Hydrophilic substances, specificaly substances with hydrocolloidal properties, more specifically carrageenan has proven satisfactorily as demonstarted by following stability data: during the storage at 60° C for 14 days the tablet prepared without carrageenan (Comparative example) contain 5.34% of degradation products related to candesartan cilexetil, while the tablet prepared with carrageenan (Example 1) contain only 1,63% of degradation products related to candesartan cilexetil.

Comparative example: Candesartan cilexetil 32 mg without carragenaan

Materials	**Per tablet**
Candesartan cilexetil	32.00 mg
Lactose monohydrate	196.80 mg
Sodium lauryl sulfate	3.20 mg
Microcristalline cellulose	64.00 mg
Povidone	9.60 mg
Aerosil	0.8 mg
Sodium starch glycolate	12.60 mg
Mg – stearate	1.00 mg
Total	320.00 mg

Claims

1. A solid pharmaceutical composition comprising a lipophilic active pharmaceutical ingredient optionally in combination with at least one another active pharmaceutical ingredients characterized in that it comprises from 2 to 20 % of a hydrophilic substance with hydrocolloidal properties.

2. The solid pharmaceutical composition according to previous claim where a hydrophilic substance with hydrocolloidal properties is a polysaccharide extracted from algae.

3. The solid pharmaceutical composition according to any of claims 1 or 2 where a hydrophilic substance with hydrocolloidal properties is carrageenan.

4. The solid pharmaceutical composition according to any of claims 1 to 3 where the lipophilic active pharmaceutical ingredient is candesartan cilexetil.

5. The solid pharmaceutical composition according to any of claims 1 to 4 where the lipophilic active pharmaceutical ingredient is candesartan cilexetil and said composition further comprises hydrochlorotiazide.

6. The solid pharmaceutical composition comprising at least one lipophilic active pharmaceutical ingredient and up to 20 % by weight of a carrageenan and from 40 to 80% by weight of one or more diluents and from 2 to 25% by weight of one or more disintegrants and up to 5% by weight of one or more binders.

7. The solid pharmaceutical composition comprising candesartan cilexetil and optionally manidipine hydrochloride or hydrochlorothiazide and up to 20 % by weight of a carrageenan and from 40 to 80% by weight of one or more diluents and from 2 to 25% by weight of one or more disintegrants and up to 5% by weight of one or more binders.

8. The solid pharmaceutical composition according to any of the previous two claims characterized in that the it comprises of from 1 to 20% by weight of candesartan

cilexetil, from 1 to 20% by weight of carrageenan, from 40 to 80% by weight of one or more diluents, from 2% to 25% by weight of one or more disintegrants and from 0,5% to 5% by weight of one or more binders.

9. The solid pharmaceutical composition according to any of the previous three claims characterized in that the it comprises from 1 to 20% by weight of candesartan cilexetil, optionally from 1% to 20% by weight of hydrochlorotiazide and from 1 to 20% by weight of carrageenan.

10. The solid pharmaceutical composition according to previous claim characterized in that it additionally comprises together from 40 to 80% by weight of lactose and starch, from 2% to 25% by weight of sodium carboxymethylcellulose and from 0,5% to 5% by weight of povidone.

11. A pharmaceutical composition in a form of a tablet, comprising between about 1% and about 10% by weight of candesartan cilexetil and between 2% and 20% of carrageenan.

12. The pharmaceutical composition according to previous claim, characterized in that amount of carrageenan is about 4%.

13. The pharmaceutical composition according to previous claim, characterized in that it additionally comprises one or more inactive ingredients selected from group consisting of lactose, starch, povidone, carboxymethylcellulose sodium and magnesium stearate..

14. Use of a composition according to any of the previous claims for the manufacturing of a medicament.

15. Use of carrageenan in the manufacturing of a stable pharmaceutical composition.

16. Use of carrageenan according to the previous claim in the manufacturing of a stable pharmaceutical composition comprising a lipophylic crystalline substance as an active pharmaceutical ingredient.

17. Use of carrageenan in the manufacturing of a stable pharmaceutical composition comprising candesartan cilexetil.

18. Process for preparing a stable pharmaceutical composition by tableting, by first providing a granulate comprising active pharmaceutical ingredient, characterized in that the carrageenan is added to the granulate before tableting.

19. Process according to previous claim, characterized in that it is made by the tableting process where main pressure is at maximum 20 kN.

20. Process according to any of the previous two claims, where the composition comprises candesartan cilexetil characterized in that it contains following steps:
    a) providing a granulate comprising candesartan cilexetil;
    b) mixing said granulate with one or more components where one of the components is carrageenan;
    c) tableting the mixture obtained in previous step

21. A method of treating hypertension by administering a pharmaceutical composition comprising candesartan cilexetil and carrageenan to the patients in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/000587

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/20 A61K45/06 A61P9/12

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 546 358 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 16 June 1993 (1993-06-16) *cf. abstract, generic formulae on page 11, and lines 11-41, example 1, on page 14, table 1 on page 17, table 3 on page 18, and claim 1*	1-6 7-21
X Y	WO 97/37688 A (TAKEDA CHEMICAL INDUSTRIES, LTD; TAMURA, NORIKAZU; SOHDA, TAKASHI; IKE) 16 October 1997 (1997-10-16) *cf. page 9, line 5 extending to page 11, line 6, page 41, lines 10-18, page 45, examples 16/17 concerning capsules and tablets, claim 1*	1-6 7-21

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2006	05/04/2006

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

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/000587

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2001/010825 A1 (SHIMIZU TOSHIHIRO ET AL) 2 August 2001 (2001-08-02) *cf. abstract, section [0007] on page 1, section [0055] on page 2, section [0108] on page 4, sections [0211]-[0216] on page 10*	1-21
Y	US 2004/131675 A1 (YAMAMOTO KEIICHI ET AL) 8 July 2004 (2004-07-08) *cf. abstract, page 3, section [0074], page 4, section [0095], page 5, sections [0108]-[0111], page 6, section [0127], page 7, section [0144], claim 1*	1-21
Y	WO 00/06126 A (TAKEDA CHEMICAL INDUSTRIES, LTD; SHIMIZU, TOSHIHIRO; SUGAYA, MASAE; NA) 10 February 2000 (2000-02-10) *cf. abstract, page 2, line 5 to page 3. line 24, page 9, lines 5-25, page 12, lines 10-13, page 29, 3rd para., page 13, 2nd para., claims 1,10,12*	1-21

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-6

The present claims 1-6 relate to an extremely large number of possible compounds/products. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the
compounds/products/, see claim 7 below. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking
into consideration the non-compliance in determining the extent of the search of claim
7 (PCT Guidelines 9.19 and 9.23).

The search of claims 1-6 was restricted to those claimed compounds/products which appear to be supported by the compounds according to page 2 and the examples cited in the description.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/000587

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INTERNATIONAL SEARCH REPORT

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