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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
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(54) **Title:** PHARMACEUTICAL COMPOSITION OF FEBUXOSTAT

(57) **Abstract:** The present invention relates to an immediate-release febuxostat composition and process of preparation for the same. It also relates to a method of treating gout and hyperuricemia using the composition of the present invention.

PHARMACEUTICAL COMPOSITION OF FEBUXOSTAT

Field of the Invention

The present invention relates to an immediate-release febuxostat composition and process of preparation for the same.

5

Background of the Invention

Febuxostat is chemically known as 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid. (U.S. Patent Nos. 5,614,520 and 6,225,474).

Febuxostat is a non-purine selective inhibitor of xanthine oxidase. It works by non-competitively blocking the channel leading to the active site on xanthine oxidase.

10 Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid. Febuxostat is a useful therapeutic agent for gout and hyperuricemia. In a comparative study between febuxostat and allopurinol, it was found that more individuals treated with febuxostat had decreased levels of uric acid. For treatment of hyperuricemia in patients
15 with gout, febuxostat is recommended at 40 mg or 80 mg once daily. No dose adjustment is necessary when administering febuxostat in patients with mild to moderate renal and hepatic impairment.

Febuxostat is commercially available as an immediate-release formulation in the form of tablets.

20

According to the Biopharmaceutics Classification System, febuxostat is classified as a Class 2 compound (low solubility, high permeability). It suffers from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism following oral administration. The therapeutic dose required to be administered must thus be
25 increased in order to obviate this disadvantage.

Hence, there exists a need in the art to develop a formulation of febuxostat having improved dissolution profile and bioavailability.

U.S. Patent No. 6,225,474 assigned to Teijin Limited discloses six crystal polymorphs of febuxostat designated as crystal A, B, C, D, E and G.

U.S. Patent No. 7,361,676 discloses a pharmaceutical preparation containing crystal A with average particle diameter from 12.9 μm to 26.2 μm .

CN 101966163 discloses dispersible tablets of febuxostat.

CN 101953814 discloses a solid preparation prepared from febuxostat and
5 medicinal adjuvants.

CN 101940562 discloses a solid preparation composed of nano-capsules of febuxostat or its medicinal salt and drug accessories.

Summary of the invention

In one aspect, the present invention relates to an immediate-release febuxostat
10 composition comprising:

- (a) an inert carrier covered with at least one layer containing febuxostat in a micronized form having an average particle size less than 50 μm , a hydrophilic polymer and, optionally, a surfactant; and
- (b) optionally one or several outer phase(s) or layer(s).

15 In one embodiment, the composition of present invention can optionally have one or more film coatings.

In another aspect, the present invention relates to a process for preparing an immediate-release febuxostat composition comprising:

- 20 a) preparing febuxostat solution or suspension in micronized form with an average particle size less than 50 μm , in a solution of hydrophilic polymer and, optionally a surfactant;
- b) applying the suspension from step a) to an inert carrier;
- c) optionally coating granules thus obtained with one or several phase(s) or layer(s).

25 Step b) is preferably carried out in a fluidized-bed granulator. The method can comprise a step in which products obtained from step b) or c) are compressed, with or without additional excipients.

The compositions according to the invention can additionally contain any excipient conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as diluents, binders, disintegrants, lubricants, glidants, surfactants, buffers, wetting agents, coloring agents, flavoring agents and combinations thereof.

The invention also provides a solution or suspension of febuxostat in micronized form having an average particle size less than 50 μm , in a solution of hydrophilic polymer and, optionally, surfactant.

In yet another aspect, there is provided a method of treating gout and hyperuricemia by administering to a person in need thereof an immediate-release febuxostat composition comprising:

- a) an inert carrier covered with at least one layer containing febuxostat in a micronized form having an average particle size less than 50 μm , a hydrophilic polymer and, optionally, a surfactant; and
- b) optionally one or several outer phase(s) or layer(s).

The pharmaceutical composition of febuxostat described herein may be administered in combination with other therapeutic agents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features and objects of the invention will be apparent from the description and examples.

Detailed Description of the Invention

The present invention relates to an immediate-release febuxostat composition comprising:

- a) an inert carrier covered with at least one layer containing febuxostat in a micronized form having an average particle size less than 50 μm , a hydrophilic polymer and, optionally, a surfactant; and
- b) optionally one or several outer phase(s) or layer(s).

The expression "in a micronized form" in this invention means a substance in a particulate form, wherein the average particle size being less than 50 μm .

The term “carrier”, as used herein, includes any excipient, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed.

The inert carrier may be hydrosoluble or hydroinsoluble. Examples of inert carriers comprise sucrose, lactose, maltodextrin, microcrystalline cellulose, pregelatinized starch, dicalcium phosphate, celphere and non-pareils. The carriers may be of any geometric shape, though spheres are particularly used for the case of uniform coating. The individual particle size of the inert carrier can be, for example, between 50 µm and 500 µm.

Febuxostat, used herein, encompasses all the polymorphic crystals, solvates, hydrates, co-crystals as well as amorphous forms of febuxostat, *i.e.*, Crystal A, B, C, D, G as disclosed in U.S. Patent No. 6,225,474 or any other stable form of febuxostat.

The hydrophilic polymers used in the invention include, but are not limited to, one or more of cellulose derivatives such as hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylcellulose calcium or combinations thereof; alginates such as ammonium alginate, sodium alginate, potassium alginate, calcium alginate, propylene glycol alginate, alginic acid; polyvinyl alcohol; povidone; crosslinked polyacrylic acid polymers such as carbomer, xanthan gum, guar gum, locust bean gum, potassium pectate, potassium pectinate, co-povidone, polysaccharide, polyalkylene oxides, polyalkyleneglycol, starch and derivatives; and mixtures thereof.

The term “surfactant” used in the composition may be amphoteric, non-ionic, cationic or anionic. Examples include, but are not limited to, sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearic alcohol, cetostearyl alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, and mixtures thereof.

Here, the expression “outer phase or layer” should be taken to mean any coating on the element (a) with the active ingredient forming a “core”. Indeed, it can be useful to have available one or several phase(s) or layer(s) on top of the coated core. The invention

thus covers a single core with one layer, but also several cores in a phase, as is the case of tablets which are formed from “cores” mixed with a phase.

This outer layer or phase comprises conventional excipients. The compositions according to the invention can additionally contain any excipient conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as diluents, binders, disintegrants, lubricants/glidants, surfactants, buffers, wetting agents, coloring agents, flavoring agents, and combinations thereof.

Examples of solvents used for preparing a solution or suspension of the febuxostat include, but are not limited to, water, methanol, ethanol, acidified ethanol, acetone, diacetone, polyols, polyethers, oils, esters, alkyl ketones, methylene chloride, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulphoxide, methylethylketone, acetonitrile, N,N-dimethylformamide, tetrahydrofuran, 0.1M NaOH, and mixtures thereof. Preferably, the solvents used in the composition include, but are not limited to, water, methylethylketone, acetone, DMSO, ethanol, 0.1M NaOH, methanol, acetonitrile, or mixtures thereof.

Examples of fillers or diluents include, but are not limited to, corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium dihydrogen phosphate dihydrates, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrans, dextrose, fructose, kaolin, lactitol, mannitol, starch and starch pregelatinized. Particularly, the fillers comprise lactose, microcrystalline cellulose, calcium hydrogen phosphate dehydrate, or a mixture thereof.

Examples of binders include, but are not limited to, povidones, starches, corn starch, pregelatinized starch, microcrystalline celluloses (MCC), silicified MCC (*e.g.*, ProsolvTMHD 90), microfine celluloses, lactose, calcium carbonate, calcium sulfate, sugar, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, stearic acid, gums, hydroxypropyl methylcelluloses or hypromelloses (*e.g.*, KluccelTMEF, MethocelTME5 premium) and other pharmaceutically acceptable substances with cohesive properties.

Examples of disintegrants include, but are not limited to, cross-linked polyvinyl pyrrolidone, corn starch, potato starch, maize starch and modified starches, agar-agar, calcium carbonate, sodium carbonate, alginic acids, cross-carmellose sodium, sodium starch glycolate, microcrystalline cellulose, and mixtures thereof.

5 Examples of lubricants and glidants that can be used in the present invention include, but are not limited to, colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, solid polyethylene glycols, sodium stearyl fumarate, silica gel and mixtures thereof and other substances with lubricating or gliding properties.

10 Examples of buffers that can be used in the present invention include, but are not limited to, phosphate, acetate, citrate, succinate and histidine buffers.

 Examples of wetting agents that can be used in the present invention include, but are not limited to, ammonium lauryl sulfate and sodium lauryl sulfate.

15 The coloring agents and flavoring agents of the present invention may be selected from any FDA approved colors and flavors for oral use.

 The compositions according to the invention comprise, in general, based on the total composition weight an inert carrier making up from 10% to 80% by weight, preferably 30% to 60% by weight, the febuxostat representing from 5% to 50% by weight, preferably from 15% to 35% by weight, the hydrophilic polymer representing from 1% to 20 50% by weight, preferably 5% to 40% by weight, the surfactant making up from 0% to 10% by weight, preferably 0.1% to 3% by weight.

 The outer layer or phase, if present, can make up to 80% by weight of the total weight, preferably up to 50% by weight.

25 In one embodiment, the composition according to the invention takes the form of tablets. This tablet preferably results from the compression of elements (a) (under the form of granules) together with an outer phase.

 In another embodiment, the composition of the invention takes the form of granules enclosed inside a capsule, for example, in gelatin, or inside a bag.

The compositions of the invention are particularly suitable for administering active ingredients by oral route.

The composition according to the invention is prepared by a process comprising spraying a solution or suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert cores. The method according to the invention consists in using the fluidized-bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension or solution of the micronized active ingredient in a solution of a hydrophilic polymer and, optionally, a surfactant.

The fluidized-bed granulation technique is widely used in the pharmaceutical industry for preparing capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient+excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art.

The invention, as has been indicated, comprises spraying a solution or suspension of an active ingredient micronized with a hydrophilic polymer onto an inert carrier. Following granulation, the granulate formed consists of crystals of, for example, lactose, which are isolated (or possibly agglomerated together by the spray solution) and particles of active ingredient and PVP adhering to the crystal surface. The granulate could similarly be constituted of coated crystals which are agglomerated, or even of such an agglomerate having received a coating.

The granulates thus obtained can, if desired, be provided with an outer coating or compressed into tablets, or form agglomerates.

The outer layer or layer is/are applied using conventional coating techniques such as coating in a pan or fluidized bed coater.

When the granulate obtained (whether subsequently coated or not) is compressed to form tablets, this step can be implemented using any conventional technique which is suitable, for example, using an alternating or rotating compressing equipment.

The tablets may further be film coated. Additional excipients such as film-forming polymers, solvents, plasticizers, antiadherents, opacifiers and optionally colorants, pigments, antifoam agents, and polishing agents can be used in coatings.

Examples of film-forming agents include, but are not limited to, cellulose derivatives such as soluble alkyl- or hydroalkyl-cellulose derivatives such as methylcelluloses, hydroxymethyl celluloses, hydroxyethyl celluloses, hydroxypropyl celluloses, hydroxymethylethyl celluloses, hydroxypropyl methylcelluloses, sodium carboxymethyl celluloses, etc.; insoluble cellulose derivatives such as ethylcelluloses and the like; dextrans; starches and starch derivatives; polymers based on carbohydrates and derivatives thereof; natural gums such as gum Arabic; xanthans; alginates; polyacrylic acids; polyvinyl alcohols; polyvinyl acetates; polyvinylpyrrolidones; polymethacrylates and derivatives thereof (Eudragit® products), chitosan and derivatives thereof; shellac and derivatives thereof; waxes and fat substances.

The coating can also be performed using any commercially available ready-to-coat preparations such as Opadry® AMB, Opadry® White, Opadry® Clear, Opadry® II, etc. Opadry® formulations generally comprise polymer, plasticizer and, if desired, pigment in a dry concentrate. OPADRY® products produce attractive, elegant coatings on a variety of tablet cores and can be used in both aqueous and organic coating procedures.

Some of the excipients are used as adjuvants to the coating process, including excipients such as plasticizers, opacifiers, antiadhesives, polishing agents, and the like.

Examples of plasticizers include, but are not limited to, castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycols, propylene glycols, triacetin, triethyl citrate, and mixtures thereof. An opacifier like titanium dioxide may also be present in an amount ranging from about 10% (w/w) to about 20% (w/w) based on the total weight of the coating.

Antiadhesives are frequently used in the film coating process to avoid sticking effects during film formation and drying. An example of an antiadhesive for this purpose is talc.

Examples of polishing agents include, but are not limited to, polyethylene glycols of various molecular weights, or mixtures thereof, talc, surfactants (e.g., glycerol

monostearate and poloxamers), fatty alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, lauryl alcohol and myristyl alcohol) and waxes (*e.g.*, carnauba wax, candelilla wax and white wax).

The present invention also encompasses suspension of the active ingredient. This
5 suspension is prepared by putting the micronized active ingredient into suspension in a solution comprising the hydrophylic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent. Next, the hydrophylic polymer is dispersed, while stirring, in the solution previously obtained. Depending on polymer solubility, this either dissolves in the solution or forms a gel or a
10 suspension having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogeneous suspension. The order of these steps can be reversed. The solvent employed can be aqueous or organic (for example, ethanol). For example, demineralized water can be used.

15 The composition of the invention may be used in treating conditions such as gout and hyperuricemia. The pharmaceutical composition of febuxostat may be administered in combination with other therapeutic agents.

The present invention is illustrated below by reference to the following example. However, one skilled in the art will appreciate that the specific methods and results
20 discussed are merely illustrative of the invention, and not to be construed as limiting the invention.

Example:

Ingredients	Percent w/w
Drug Coated Granules (Part – A)*	
Febuxostat #	24.34
Pregelatinized Starch	47.84
Polyvinylpyrrolidone	12.17
Sodium Lauryl Sulphate	1.06
Purified Water	
Total	85.41
Blend (Part – B)	
Drug Coated Granules (From Part – A)	77.65
Microcrystalline Cellulose	13.83
Cross Linked Polyvinylpyrrolidone	3.87
Colloidal Silicon Dioxide	0.48
Sodium Stearyl Fumarate	0.97
Core Tablet Weight	96.80
Film Coating	
Opadry®	3.19
Purified Water	q.s.

* Includes 10% extra to compensate the losses during coating process.

Average particle size <50.00 micron

Procedure:

- 5 1. Polyvinylpyrrolidone was dissolved in purified water and febuxostat was dispersed under continuous stirring. Drug dispersion was passed through a colloid mill.
2. Sodium lauryl sulphate was dissolved in purified water and transferred to dispersion of step 1.
- 10 3. Pregelatinized starch was sifted through suitable mesh.
4. Pregelatinised starch of step 3 was coated with the dispersion of step 2 in a fluid bed processor.
5. The granules were dried to achieve desired LOD and passed through suitable mesh.
- 15 6. Microcrystalline cellulose, crospovidone and colloidal silicon dioxide were sifted through suitable mesh and blended with granules of step 5 in suitable blender.

7. Sodium stearyl fumarate was sifted through suitable mesh and blended with the blend of step 6.
8. The blend of step 7 was compressed.
9. The film coating suspension was prepared and step 8 core tablets were coated.
- 5 10. Tablets were packed in HDPE and blister pack.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention.

We claim:

- 1 1. An immediate-release febuxostat composition comprising an inert carrier covered
2 with at least one layer containing febuxostat in a micronized form having an
3 average particle size less than 50 μm , a hydrophilic polymer and, optionally, a
4 surfactant.
- 1 2. A composition according to claim 1 further comprising at least one outer phase or
2 layer.
- 1 3. An immediate-release febuxostat composition according to claim 1, wherein the
2 inert carrier is hydrosoluble or hydroinsoluble.
- 1 4. An immediate-release febuxostat composition according to claim 1, wherein the
2 inert carrier comprises one or more of sucrose, lactose, maltodextrin,
3 microcrystalline cellulose, pregelatinized starch, dicalcium phosphate, celphere or
4 non-pareils.
- 1 5. An immediate-release febuxostat composition according to claim 1, wherein the
2 hydrophilic polymer comprises one or more of cellulose derivatives; alginates,
3 polyvinyl alcohol, povidone, crosslinked polyacrylic acid polymers, xanthan gum,
4 guar gum, locust bean gum, potassium pectate, potassium pectinate, co-povidone,
5 polysaccharide, polyalkylene oxides, polyalkyleneglycol, starch and derivatives;
6 and mixtures thereof.
- 1 6. An immediate-release febuxostat composition according to claim 1, wherein the
2 surfactant used in the composition is amphoteric, non-ionic, cationic or anionic.
- 1 7. An immediate-release febuxostat composition according to claim 2, wherein the
2 outer layer or phase comprises conventional excipients such as diluents, binders,
3 disintegrants, lubricants/glidants, surfactants, buffers, wetting agents, coloring
4 agents, flavoring agents and combinations thereof.
- 1 8. A process for preparing an immediate-release febuxostat composition comprising:
2 a) preparing febuxostat solution or suspension in micronized form with an
3 average particle size less than 50 μm , in a solution of hydrophilic polymer and,
4 optionally a surfactant;

- 5 b) applying the suspension from step a) to an inert carrier.
- 1 9. A process according to claim 8, further comprising the step of coating the granules
2 obtained in step b) with at least one phase or layer.
- 1 10. A method of treating gout and hyperuricemia by administering to a person in need
2 thereof an immediate-release febuxostat composition comprising an inert carrier
3 covered with at least one layer containing febuxostat in a micronized form having
4 an average particle size less than 50 μm , a hydrophilic polymer and, optionally, a
5 surfactant.
- 1 11. A method of treating gout and hyperuricemia according to claim 10, wherein the
2 immediate-release febuxostat composition further comprises at least one outer
3 phase or layer.
- 1 12. A method of treating gout and hyperuricemia according to claim 10, wherein the
2 immediate-release febuxostat composition is administered in combination with
3 other therapeutic agents.

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2012/052371

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/16 A61K31/426 A61P19/06 ADD.				
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 practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
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Y	CN 101 780 073 A (CHONGQING SHENGHUAXI PHARMA CO) 21 July 2010 (2010-07-21) paragraph [0023] - paragraph [0034] paragraph [0050] - paragraph [0052] paragraph [0059] - paragraph [0061] paragraph [0071] - paragraph [0073] -----	1-12		
Y	CN 101 474 175 A (CHONGQING PHARMACEUTICAL RES I [CN]) 8 July 2009 (2009-07-08) the whole document ----- -/--	1-12		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> 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 application or patent 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			
17 August 2012	28/08/2012			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Giró, Annalisa			

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2012/052371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/IB2012/052371

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