Title: MULTICOMPONENT CRYSTALLINE SYSTEM COMPRISING DEFERASIROX AND ISONICOTINAMIDE AND A PROCESS FOR THE PREPARATION THEREOF

Abstract: The present invention refers to a multicomponent crystalline system (co-crystal) comprising a compound of formula (I) (4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid; INN: Deferasirox) formula (I) and a compound of formula (2) (isonicotinamide; pyridine-4-carboxamide) formula (2), as well as to a process for obtaining the same.

Published:

— with international search report (Art. 21(3))
Multicomponent crystalline system comprising Deferasirox and Isonicotinamide and a process for the preparation thereof

Description

Deferasirox (4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid) is an orally active iron chelator that is indicated in the treatment of iron overload in transfusion dependent anemias, in particular thalassemia major, thalassemia intermediate and in sickle cell disease to reduce iron-related morbidity and mortality. Deferasirox can also be used in the treatment of hemochromatosis.

The active ingredient Deferasirox is sold under the trademark EXJADE® as dispersible tablet for oral administration and comprises Deferasirox free drug substance as active ingredient.

According to the marketing authorization EXJADE® is indicated for the treatment of chronic iron overload due to frequent blood transfusions (7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. EXJADE® is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (>7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
- in patients with other anemias aged 2 years and older.

EXJADE® is dispersed by stirring in a glass of water or orange or apple juice (100 to 200 ml) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be resuspended in a small volume of water or juice and swallowed.

Thus, it is important that Deferasirox as active ingredient has a very good solubility in water, which is not the case. A suspension is formed when the dispersible tablet is dispersed in water. Thus, it is possible that a patient in need of Deferasirox does not take up the entire active ingredient being present in the dispersible tablet. It might be possible that a residue remains not being administered to the patient.

WO 2008/065123 refers to several crystalline forms of Deferasirox. Several forms and in particular form A are characterized by XRPD. The solubility in water of the crystalline forms of Deferasirox disclosed is poor.

Thus, the technical problem arises to modify the prior art in order to find an administration form of Deferasirox having an improved solubility in water. However, said administration form must be stable in an environment having enhanced relative humidity like tropical countries.
The technical problem underlying the present invention is solved by a multicomponent crystalline system (co-crystal) comprising a compound of formula 1 (4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid; INN: Deferasirox)

and a compound of formula 2 (Isonicotinamide; pyridine-4-carboxamide)

Deferasirox is an achiral compound, since it does not bear a chiral center. Moreover, the second compound isonicotinamide is also referred to as co-crystal former.

In the context of the present invention isonicotinamide is a co-crystal former being solid at ambient temperature (in contrast to a solvate in which the second component would be liquid at ambient temperature). Thus, the multicomponent crystalline system of the present invention can be regarded as being a co-crystal.

In the context of the present invention, ambient temperature is room temperature, being preferably 20 to 30 °C and most preferably 20 to 25 °C.
Preferably, the multicomponent crystalline system exhibits a molar ratio of the compound of formula 1 and the compound of formula 2 is in the range of from 1:0.75 to 1:1.25. Even more preferred, the molar ratio of the compound of formula 1 and the compound of formula 2 is in the range of from 1:0.8 to 1:1.2, preferably of from 1:0.9 to 1:1.1 and most preferred approximately 1:1.

Preferably, the multicomponent crystalline system according to the present invention has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKa radiation)) at 9.6, 14.6, 15.6 and / or 24.4°, preferably showing all of these peaks. Even more preferred, the multicomponent crystalline system has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKa radiation)) at 4.9, 9.6, 13.7, 14.6, 15.6, 24.4, 26.1 and / or 26.2°, preferably showing all of these peaks. A respective XRPD pattern is shown in figure 1.

However, the most important advantage of the multicomponent crystalline system of this invention is the dramatically enhanced aqueous solubility. The aqueous solubility of the Deferasirox was determined under the same conditions and according to the same protocol as the solubility of the multicomponent crystalline system (co-crystals).

The aqueous solubility of Deferasirox free drug substance and the multicomponent crystalline system of the present invention (Deferasirox - Isonicotinamide co-crystal) was determined in water at ambient temperature after about three days of suspension equilibration using HPLC for the determination of the concentration in the filtered solution. The solubility of Deferasirox free drug substance was found to be below the limit of detection which was estimated to about 1 microgram per ml, whereas the solubility of the Deferasirox - Isonicotinamide co-crystal was found to be about 32 microgram per ml.

Surprisingly, the solubility in water of the multicomponent crystalline system of the present invention is significantly higher than the solubility of Deferasirox free drug substance. The higher solubility of the multicomponent crystalline system is advantageous when formulated as disintegrating tablet.

It is known that the anhydrous form A of Deferasirox converts to a hydrate form upon exposure to high relative humidity, therefore anhydrous Deferasirox is hygroscopic. The multicomponent crystalline system described here is characterized in that it has good hygroscopic properties, i.e. absorb little water at high relative humidity. This is evident from table 1 below, which compares the water contents of the multicomponent crystalline system and Deferasirox free drug substance at 50 % and 95% relative humidity. The data originate from dynamic water vapor adsorption measurements. The water vapor sorption measurement is a suitable method for investigating the hygroscopic properties of solid substances. Water vapor sorption measurements can be carried out in different ways. In general, in this connection, a small sample of ca. 10-30 mg is introduced into a microbalance in a suitable sample carrier. The sample is then exposed to different relative humidities in accordance with a defined program, the change in the sample mass being simultaneously recorded over the time. As a result, insights into the hygroscopic behavior of a substance can be obtained. Both multicomponent crystalline system of the present inven-
tion and also Deferasirox free drug substance were investigated using this method and it was established that the Deferasirox free drug substance adsorbs significantly more water under identical measurement conditions and is thus more hygroscopic. It has been found that for example the multicomponent crystalline system of the present invention at 50 % relative humidity contains only ca. 0.1 % water, and after four hours at 95 % relative humidity absorbs only just ca. 0.2% more water than at 50% relative humidity, the latter value corresponding approximately to the standard humidity conditions in central Europe. Figure 2 illustrates that, when measured under identical conditions, the Deferasirox Isonicotinamide co-crystal shows substantially improved properties with respect to its hygroscopicity, because it is much less prone to water uptake than the Deferasirox Form A when exposed to high relative humidity conditions.

Table 1: Results of the water vapor sorption measurements

<table>
<thead>
<tr>
<th></th>
<th>H₂O content at 50% r.h.</th>
<th>H₂O content at 95% r.h.</th>
</tr>
</thead>
<tbody>
<tr>
<td>multicomponent crystalline system of the present invention</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Deferasirox free drug substance</td>
<td>0.5%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

This result, in particular the combination of improved solubility and better hygroscopic properties, is unexpected for the person skilled in the art and cannot be deduced from the prior art. Consequently, the multicomponent crystalline system of the present invention offers a profile of properties which is advantageous for use in medicaments and preferably in disintegrating tablets.

A further aspect of the present invention is the multicomponent crystalline system and the respective pharmaceutical composition for use in the treatment of iron overload in transfusion dependent anemias, in particular thalassemia major, thalassemia intermediate and/or in sickle cell disease to reduce iron-related morbidity and mortality and/or in the treatment of hemochromatosis.

Preferably, the multicomponent crystalline system and the respective pharmaceutical composition can be used for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia being preferably major aged 6 years and older.

The multicomponent crystalline system of the present invention and the respective pharmaceutical composition can also be used for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate, preferably in the following patient groups:
- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
Another object of the present invention is a process for obtaining the multicomponent crystalline system of the present invention comprising the steps of:

a) providing a compound of formula 1 (INN: Deferasirox) in a suitable solvent or a mixture of solvents;
b) adding a compound of formula 2 (Isonicotinamide) to the mixture of step a);
c) optionally concentrating the composition of step b);
d) crystallizing;
e) optionally equilibrating the obtained suspension of step d); and
f) isolating the obtained precipitate.

Preferably, the molar ratio of the compound of formula 1 in step a) and the compound of formula 2 in step b) is in the range from 1:0.75 to 1:5.
Preferably, in step b) the compound of formula 1 is provided in solid form, or as a solution in an ether, an alcohol, a ketone, an acetate, of mixture of solvents optionally containing water.

Preferably, the solvent used in step a) is an organic solvent such as an alcohol, ether or ketone (e.g. tetrahydrofuran, acetone, methanol, ethanol, propanol, butanol). Preferably, the solvent is a mixture of tetrahydrofuran, ethanol, methanol and/or acetone.

Solutions or suspension according to steps a) and/or b) preferably are concentrated solutions. Preferably, the solvent is an organic solvent such as an alcohol, ether or ketone (e.g. tetrahydrofuran, acetone, methanol, ethanol, propanol, butanol the solvent is a mixture of tetrahydrofuran, ethanol, methanol and/or acetone.

In a further preferred embodiment, in step d) and/or e) seed crystals are added.

The herein described multicomponent crystalline system shows good kinetic and thermodynamic stability.

The multicomponent crystalline system is generally obtained as a fine powder with typical particle size distributions with the median size between 1 and 50 µm, preferably between 1 to 10 µm. This particle size range ensures a fast dissolution profile, while retaining the favorable handling properties in the formulation process.

However, the most important advantage of the multicomponent crystalline system of the present invention is the dramatically enhanced aqueous solubility.

A further aspect of the present invention is a pharmaceutical composition comprising the multicomponent crystalline system of the present invention and optionally one or more pharmaceutically acceptable excipients.

Oral formulations may be solid formulations such as capsules, tablets, pills and troches, or a liquid suspension formulation.

The crystalline composition according to the invention may be used directly as powders (micronized particles), granules, suspensions, or they may be combined together with other pharmaceutically acceptable ingredients in admixing the components and optionally finely divide them, and then filling capsules, composed for example from hard or soft gelatin, compressing tablets, pills or troches, or suspend in suspensions. Coatings may be applied after compression to form pills.

Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders such as natural or synthetic polymers, excipients, disintegrants, lubricants, surfactants, sweetening and other flavouring agents, coating materials, preserva-
tives, dyes, thickeners, adjuvants, antimicrobial agents and carriers for the various formulation types.

Examples for binders are gum tragacanth, acacia, starch, gelatin, and biological degradable polymers such as homo- or co-polyesters of dicarboxylic acids, alkylene glycols, polyalkylene glycols and/or aliphatic hydroxyl carboxylic acids; homo- or co-polyamides of dicarboxylic acids, alkylene diamines, and/or aliphatic amino carboxylic acids; corresponding polyester-polyamide-co-polymers, polyanhydrides, polyorthoesters, polyphosphazene and polycarbonates. The biological degradable polymers may be linear, branched or crosslinked. Specific examples are poly-glycolic acid, poly-lactic acid, and poly-d,l-lactide/glycolide. Other examples for polymers are water-soluble polymers such as polyoxaalkylenes (polyoxaethylene, polyoxapropylene and mixed polymers thereof, poly-acrylamides and hydroxylalkylated polyacrylamides, poly-maleic acid and esters or-amides thereof, poly-acrylic acid and esters or-amides thereof, poly-vinylalcohol und esters or-ethers thereof, poly-vinylimidazole, poly-vinylpyrrolidon, and natural polymers like chitosan, carragenan or hyaluronic acid.

Examples for excipients are phosphates such as dicalcium phosphate.

Examples for disintegrants are croskarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, sodium starch glycolate or alginic acid.

Surfactants may be anionic, cationic, amphoteric or neutral. Examples for surfactants are lecithin, phospholipids, octyl sulfate, decyl sulfate, dodecyl sulfate, tetradecyl sulfate, hexadecyl sulfate and octadecyl sulfate, Na oleate or Na caprate, 1-acylaminoethane-2-sulfonic acids, such as 1-octanoylaminoethane-2-sulfonic acid, 1-decanoylaminoethane-2-sulfonic acid, 1-dodecanoylaminoethane-2-sulfonic acid, 1-tetradecanoylaminoethane-2-sulfonic acid, 1-hexadecanoylaminoethane-2-sulfonic acid, and 1-octadecanoylaminoethane-2-sulfonic acid, and taurocholic acid and taurodeoxycholic acid, bile acids and their salts, such as cholic acid, deoxycholic acid and sodium glycocholates, sodium caprate or sodium laurate, sodium oleate, sodium lauryl sulphate, sodium cetyl sulphate, sulfated castor oil and sodium dioctyl-sulfosuccinate, cocamidopropylbetaine and laurylbetaine, fatty alcohols, cholesterol, glycerol mono- or -distearate, glycerol mono- or -dioleate and glycerol mono- or -dipalmitate, and polyoxyethylene stearate.

Examples for sweetening agents are sucrose, fructose, lactose or aspartam.

Examples for flavouring agents are peppermint, oil of wintergreen or fruit flavours like cherry or orange flavour.

Examples for coating materials are gelatin, wax, shellac, sugar or biological degradable polymers.
Examples for preservatives are methyl or propylparabens, sorbic acid, chlorobutanol, phenol and thimerosal.

Examples for adjuvants are fragrances.

Examples for thickeners are synthetic polymers, fatty acids and fatty acid salts and esters and fatty alcohols.

Examples for solid carriers are talc, clay, microcrystalline cellulose, silica, alumina and the like.

The formulation according to the invention may also contain isotonic agents, such as sugars, buffers or sodium chloride.

Preferably, the pharmaceutical composition comprising the multicomponent crystalline system is a dispersible tablet. The multicomponent crystalline system of the present invention may also be formulated as effervescent tablet or powder, which can disintegrate in an aqueous environment to provide a drinking solution.

The most preferred route is oral administration. The dosages may be conveniently presented in a unit dosage form and prepared by any of the methods well-known in the art of pharmacy

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

The multicomponent crystalline system of the present invention and its formulations, respectively, can be also being administered in combination with other therapeutic agents being effective to treat a given condition and/or to provide a combination therapy.

Abbreviations:
- HPLC: high pressure liquid chromatography
- NMR: nuclear magnetic resonance
- TGA: thermogravimetric analysis
- r.h.: relative humidity (air, if not indicated otherwise)
- v/v: volume by volume
- XRPD: X-ray powder diffraction
- DVS: dynamic vapor sorption
Instrumental
X-ray powder diffraction:
The measurements were carried out with a Stoe Stadi P with a Mythen K Detector and Cu-Kα1 radiation. Measurement conditions: transmission; 40 kV and 40 mA tube power; curved Ge monochromator; 0.02°2Θ step size, 12 s step time, 1.5-50.5° in 2Θ scanning range; detector mode: step scan; 1°2Θ detector step; standard sample preparation: 10 to 20 mg sample was placed between two acetate foils; sample holder: Stoe transmission sample holder; the sample was rotated during the measurement.

Generally, the 2Θ values are accurate within an error of ±0.1-0.2°. The relative peak intensities can vary considerably for different samples of the same crystalline form because of different preferred orientations of the crystals.

Thermogravimetric Analysis (TGA):
TGA was performed with a TA Instruments TGA Q5000 instrument at a heating rate of 10° per minute from 25 to 300°C.

1H-NMR:
The 1H-NMR spectra were recorded on a Bruker DPX 300 spectrometer. Solvent: D6-DMSO

Solubility determinations:
Solubility determinations were carried out in pure water at 25±2°C. Suspensions with about 50 mg the solid form, either the co-crystal of the present invention or deferasirox free drug substance in 7 mL water were prepared an equilibrated for three days before the solution phase was filtered off and tested by HPLC.

HPLC:
HPLC was carried out on an Agilent 1100 HPLC chromatograph equipped with a UV-vis detection unit. The column type used was a Waters XTerra MS C18, 100 x 4.6 mm, 5 μm (FK-CC01 F). The applied gradient method with eluent A (water containing 1% of trifluoroacetic acid) and eluent B (acetonitrile) was as follows: At t = 0 minutes: 95% A, 5% B, 20 minutes: 5% A, 95% B, 20.5 minutes: 95% A and 5% B, 25 minutes: 95% A, 5% B. The applied flow rate was 1.0 mL per minute, the injection volume was 10 microliter and the detection wavelength was 254 nm.

Water vapor adsorption measurements (DVS)
Dynamic water vapor adsorption measurements were carried out using an SPS1 1 100n instrument, manufactured by "Projekt Messtechnik" in Ulm, Germany. For this, ca. 20 mg of the sample were weighed into an aluminum support and this was inserted into the measurement chamber of the instrument. The sample was then subjected to preselected relative humidities in accordance with a defined program, the change in mass being determined over the time. The following measurement program was used: 50% r.h. constant for two hours, then changing the relative humidity to 0% r.h., then changing the relative humidity to 96% r.h., constant at 96% r.h.
for four hours and then changing the relative humidity to 50% r.h. and then constant at 50% r.h.
for one hour. The change rates set were in each case 5% per hour.

Solvents: For all experiments, Fluka or Sigma Aldrich grade solvents are used. Selected sol-
vents are dried using 3 or 4 Å molecular sieves.

The following examples illustrate the invention.

Example 1
To 51 mg isonicotinamide and 150 mg Deferasirox was added 100 µl methanol. This mixture
was vigorously ground to dryness in an agate mortar. Then another 100 µl methanol was added
and grinding was carried out. Investigation of the solid material by XRPD shows that an new
solid form that is still containing some Deferasirox form A is obtained. The mixture of the multi-
component crystalline system with Deferasirox form A was further processed by addition of 4 ml
of acetone. The resulting suspension was shortly heated to reflux temperature and then stirred
at r.t in an open vial allowing about 3 ml of the solvent to evaporate before the solid was sepa-
rated by filtration. Investigation of the resulting crystalline material by XRPD shows a powder
pattern as shown in Figure 1 with peak locations as provided in table 2. Further analysis by H-
NMR reveals a molar ratio of about 1:1 of Deferasirox and Isonicotinamide.

Example 2
882 mg of Deferasirox and 290 mg of isonicotinamide are dissolved in a mixture of 15 ml ace-
tone and 3 ml THF by shortly heating to reflux temperature. Let the solution cool to room tem-
perature and evaporate the solvents under a flow of nitrogen with a flow rate about 50 ml per
minute. To the dry residue 5 ml acetone is added and the resulting suspension is stirred at
room temperature for two hours before the solid is filtered off. The obtained crystalline material
is investigated by XRPD, TGA, H-NMR and dynamic vapor sorption analysis. H-NMR spectro-
copy of the solid material indicates a molar ratio of Deferasirox to Isonicotinamide of about 1:1.
Thermogravimetric analysis shows no significant mass loss below 150°C and therefore we con-
clude that the co-crystal is neither a solvate nor a hydrate. Powder X-ray diffraction shows a
XRPD pattern that is characteristic for the Deferasirox - Isonicotinamide co-crystal as depicted
figure 1 and with peak locations as set out in table 2. The aqueous solubility at room tempera-
ture is tested by equilibrating a suspension of about 50 mg of the solid product in 7 ml purified
water over three days. Then suspension is filtered and the concentration in the solution deter-
mined by HPLC. The solubility in water at 25±2°C is about 32 microgram per ml. The dynamic
water vapor sorption diagram is exemplified in figure 2 and the water content at 50% and 95%
relative humidity is given in table 1.
Table 2: XRPD peak locations for the Deferasirox Isonictinamide co-crystal

<table>
<thead>
<tr>
<th>2Θ angle</th>
<th>d-spacing Å</th>
<th>Qualitative intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9</td>
<td>18.2</td>
<td>w</td>
</tr>
<tr>
<td>9.6</td>
<td>9.2</td>
<td>s</td>
</tr>
<tr>
<td>10.8</td>
<td>8.2</td>
<td>w</td>
</tr>
<tr>
<td>12.1</td>
<td>7.3</td>
<td>vw</td>
</tr>
<tr>
<td>12.8</td>
<td>6.9</td>
<td>vw</td>
</tr>
<tr>
<td>13.7</td>
<td>6.4</td>
<td>w</td>
</tr>
<tr>
<td>14.6</td>
<td>6.0</td>
<td>m</td>
</tr>
<tr>
<td>15.6</td>
<td>5.69</td>
<td>vs</td>
</tr>
<tr>
<td>16.0</td>
<td>5.53</td>
<td>m</td>
</tr>
<tr>
<td>16.2</td>
<td>5.45</td>
<td>m</td>
</tr>
<tr>
<td>17.5</td>
<td>5.05</td>
<td>m</td>
</tr>
<tr>
<td>17.9</td>
<td>4.95</td>
<td>m</td>
</tr>
<tr>
<td>19.4</td>
<td>4.58</td>
<td>w</td>
</tr>
<tr>
<td>19.8</td>
<td>4.47</td>
<td>w</td>
</tr>
<tr>
<td>21.2</td>
<td>4.19</td>
<td>w</td>
</tr>
<tr>
<td>21.7</td>
<td>4.09</td>
<td>w</td>
</tr>
<tr>
<td>22.7</td>
<td>3.91</td>
<td>w</td>
</tr>
<tr>
<td>24.4</td>
<td>3.65</td>
<td>s</td>
</tr>
<tr>
<td>25.5</td>
<td>3.49</td>
<td>m</td>
</tr>
<tr>
<td>25.9</td>
<td>3.44</td>
<td>m</td>
</tr>
<tr>
<td>26.1</td>
<td>3.41</td>
<td>s</td>
</tr>
<tr>
<td>26.2</td>
<td>3.40</td>
<td>s</td>
</tr>
<tr>
<td>26.6</td>
<td>3.35</td>
<td>vw</td>
</tr>
<tr>
<td>26.9</td>
<td>3.31</td>
<td>m</td>
</tr>
<tr>
<td>28.2</td>
<td>3.16</td>
<td>m</td>
</tr>
<tr>
<td>29.0</td>
<td>3.07</td>
<td>w</td>
</tr>
<tr>
<td>30.8</td>
<td>2.90</td>
<td>w</td>
</tr>
<tr>
<td>32.3</td>
<td>2.77</td>
<td>w</td>
</tr>
<tr>
<td>33.9</td>
<td>2.64</td>
<td>vw</td>
</tr>
<tr>
<td>Value</td>
<td>Factor 1</td>
<td>Factor 2</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>35.4</td>
<td>2.53</td>
<td>w</td>
</tr>
<tr>
<td>38.1</td>
<td>2.36</td>
<td>vw</td>
</tr>
</tbody>
</table>

Vs = very strong, s = strong, m = medium, w = weak, vw = very weak
Claims

1. A multicomponent crystalline system (co-crystal) comprising a compound of formula 1 (4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid; INN: Deferasirox) and a compound of formula 2 (Isonicotinamide; pyridine-4-carboxamide)

2. The multicomponent crystalline system according to claim 1, characterized in that the molar ratio of the compound of formula 1 and the compound of formula 2 is in the range of from 1:0.75 to 1:1.25.

3. The multicomponent crystalline system according to claim 1 or 2, characterized in that it has an XRPD pattern with at least one characteristic peak (expressed in 2\(\theta\) ± 0.2°) at 9.6, 14.6, 15.6 and/or 24.4°.
4. The multicomponent crystalline system according to claim 3, characterized in that it has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKa radiation)) at 4.9, 9.6, 13.7, 14.6, 15.6, 24.4, 26.1 and/or 26.2°.

5. The multicomponent crystalline system according to at least one of claims 1 to 4 for use in the treatment of iron overload in transfusion dependent anemias, in particular thalassemia major, thalassemia intermediate and/or in sickle cell disease to reduce iron-related morbidity and mortality and/or in the treatment of hemochromatosis.

6. A process for obtaining the crystalline composition according to at least one of the claims 1 to 5 comprising the steps of:

a) providing a compound of formula 1 (INN: Deferasirox)

\[
\text{formula 1}
\]

in a suitable solvent or a mixture of solvents;

b) adding a compound of formula 2 (Isonicotinamide)

\[
\text{formula 2}
\]
to the mixture of step a);

c) optionally concentrating the composition of step b);
d) crystallizing;
e) optionally equilibrating the obtained suspension of step d); and
f) isolating the obtained precipitate.

7. The process according to claim 6, characterized in that the molar ratio of the compound of formula 1 in step a) and the compound of formula 2 in step b) is in the range from 1:0.75 to 1:5.

8. The process according to claim 6 or 7, characterized in that in step b) the compound of formula 1 is provided in solid form, or as a solution in an ether, an alcohol, a ketone, an acetate, of mixture of solvents optionally containing water.

9. The process according to at least one of claims 6 to 8, characterized in that in step d) and/or e) seed crystals are added.

10. A pharmaceutical composition comprising the multicomponent crystalline system according to at least one of the claims 1 to 5 and optionally one or more pharmaceutically acceptable excipients.
Figure 2: Dynamic Vapor Sorption behavior of the Deferasirox Isonicotinamide co-crystal and the Deferasirox Form A. The dashed line reflects the applied measurement program which involves relative humidity change rate of 5% per hour and phases of constant humidity. The dash-dot line is the result obtained for Deferasirox Form A and the continuous line is the result for the Deferasirox Isonicotinamide co-crystal both measured under identical conditions.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D249/08 A61K31/4196 A61P7/00

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>wo 2009/130604 A2 (ACTAVIS GROUP PTC EHF [IS] ; NEELA PRAVEEN KUMAR [IN] ; CHARUGUNDLA KISH) 29 October 2009 (2009-10-29) claims ; examples</td>
<td>1-10</td>
</tr>
<tr>
<td>Y</td>
<td>wo 2008/065123 A2 (NOVARTIS AG [CH] ; MUTZ MICHAEL [DE]) 5 June 2008 (2008-06-05) claims ; examples</td>
<td>1-10</td>
</tr>
<tr>
<td>Y</td>
<td>NAR RODRIGUEZ-HORNEDO ET AL: &quot;Cocrystal s: Design, Properties and Formati on Mechanisms&quot;, 2 October 2006 (2006-10-02) , ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY, XX, XX, PAGE(S) 615 - 635, XP008095117, the whole document</td>
<td>1-10</td>
</tr>
</tbody>
</table>

[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 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 person skilled in the art

*Z* document member of the same patent family

Date of the actual completion of the international search

6 September 2013

Date of mailing of the international search report

13/09/2013

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

Gavri l i u, Dani el a
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>US 2011097413 A1</td>
<td></td>
<td>28-04-2011</td>
</tr>
<tr>
<td>WO 2009130604 A2</td>
<td></td>
<td>29-10-2009</td>
</tr>
<tr>
<td>WO 2008065123 A2</td>
<td>05-06-2008</td>
<td>AU 2007327585 A1</td>
</tr>
<tr>
<td>CA 2670313 A1</td>
<td></td>
<td>05-06-2008</td>
</tr>
<tr>
<td>EP 2099775 A2</td>
<td></td>
<td>16-09-2009</td>
</tr>
<tr>
<td>JP 2010511012 A</td>
<td></td>
<td>08-04-2010</td>
</tr>
<tr>
<td>KR 20090085081 A</td>
<td></td>
<td>06-08-2009</td>
</tr>
<tr>
<td>RU 2009124593 A</td>
<td></td>
<td>10-01-2011</td>
</tr>
<tr>
<td>US 2010056590 A1</td>
<td></td>
<td>04-03-2010</td>
</tr>
<tr>
<td>US 2012203007 A1</td>
<td></td>
<td>09-08-2012</td>
</tr>
<tr>
<td>WO 2008065123 A2</td>
<td></td>
<td>05-06-2008</td>
</tr>
</tbody>
</table>