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71. **SOLICITANTE** BRISTOL - MYERS SQUIBB COMPANY

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☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Protocolo No. 19358
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo Cular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Tarjeta de Propietarios

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

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(54) Title: PEDIATRIC FORMULATION OF GATIFLOXACIN

(57) Abstract: There is provided in accordance with the present invention the quinolone antibacterial gatifloxacin adequately taste-masked so that it can be utilized for pediatric formulations. A crystalline co-precipitate of gatifloxacin and one or both of stearic acid and palmitic acid in a narrow weight ratio has been found to effectively mask the bitter taste of gatifloxacin. The taste of gatifloxacin is effectively masked in the mouth and in aqueous suspension through a full dosage cycle, typically fourteen days. Gatifloxacin in the subject crystalline co-precipitates has been found to be readily available for absorption from the stomach.

PEDIATRIC FORMULATION OF GATIFLOXACIN

REFERENCE TO RELATED APPLICATIONS

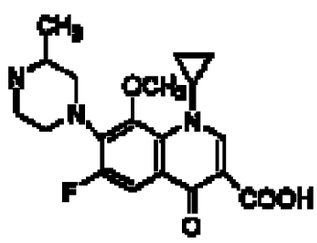
This application claims the benefit of U.S. Provisional Application Serial Number 60/299,625 filed June 20, 2001.

FIELD OF THE INVENTION

The present invention relates to gatifloxacin suitably taste-masked so that it can be utilized in oral dosage forms, particularly for pediatric formulations.

BACKGROUND OF THE INVENTION

Gatifloxacin, chemically 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, is represented by the following structure:



Gatifloxacin is a broad-spectrum quinolone antibacterial that is disclosed and claimed in U.S. Patent No. 4,980,470. U.S. Patent No. 5,043,450 discloses gatifloxacin isolated as the hemihydrate. U.S. Patent No. 5,880,283 discloses a sesquihydrate crystalline form of gatifloxacin that is advantageous over the hemihydrate in pharmaceutical manufacturing. Regardless of the particular form of gatifloxacin, typical of quinolone compounds, it has an extremely bitter taste.

It is recognized that quinolone antibacterials, such as gatifloxacin, have primary application in the treatment of infections in children. Those antibacterials that have a bitter taste are at a considerable disadvantage for pediatric use since many

pediatric preparations are in liquid form for ease of administration. Such therapeutic agents can only be administered in liquid dosage forms, including those constituted from dry powder or granules, if the formulations made therefrom have at least an acceptable taste to pediatric patients. Typically, such liquid preparations are available in the form of powders or granules that are mixed with water by a pharmacist at the time of dispensing to form a suspension in a flavored vehicle. The fine particles or granules of active substance in such preparations must either remain suspended in the liquid vehicle or be readily re-dispersed therein simply by shaking the container.

One disadvantage to pediatric suspensions as described above is that, in order to be readily suspended in an aqueous vehicle, the particles/granules of therapeutic agent are very fine. The fineness of the particles exposes a very large surface area to the aqueous vehicle. As a result, leaching of the therapeutic agent can occur, particularly over time. This phenomenon can take place regardless of the mechanism of binding utilized to mask the taste of the therapeutic agent, for example micro-encapsulation. In addition to effectively masking the taste of the therapeutic agent, the binding or coating means employed must maintain the integrity of the granules or particles in the mouth because any appreciable solubilization or leaching of the therapeutic agent by the saliva in the mouth will potentially negate the acceptable flavor of the preparation. Further, although the means of masking the taste of the therapeutic agent must maintain its integrity in the vehicle over a normal course of treatment and in the mouth, it must readily release the therapeutic agent in the stomach for absorption in order for it to be efficacious.

Numerous techniques are known in the art for masking the taste of bitter therapeutic agents. For example, Romanian Patent No. 88836, published March 31, 1986, discloses a process for masking the bitter taste of erythromycin comprising co-precipitation with stearic acid in a ratio of 1:10 utilizing acetone as the common solvent at a temperature not exceeding 40° C. Tablets prepared from the product may be chewed or suspended in a liquid, typically water, for administration. Various other representative techniques focus on the particular taste-masking substance that is mixed with, coated onto or otherwise combined with the bitter-tasting active

medicament. Examples of such substances include: acidic phospholipid or lysophospholipid, EP 0 631 787 B1; tocopherol polyethyleneglycol succinate, USP 5,891,469; certain ion-exchange resins, WO 01/05431 A1; and cubonic acid, a salt or derivative thereof, USP 5,808,076. USP 5,622,978 discloses amorphous co-precipitates of dihydropyridines and a polymer, such as polyvinyl pyrrolidone, that are administered by dispersing in water. It is stated that the co-precipitates are formed by techniques to minimize crystallinity as crystallinity has a negative effect on bioavailability.

There are also a number of teachings of techniques for coating a bitter-tasting medicament with a waxy substance and then forming a powder therefrom, typically by spray drying, heat-assisted solvent removal and the like. USP 5,405,617 discloses a method of taste-masking a bitter pharmaceutical by admixing it with stearyl stearate in the molten state and spray congealing to form a powder. European application EP 0 855 183 A2 discloses a similar process wherein a quinoline derivative and a fatty acid are combined in a blender at a temperature between 30° and 140° C and blended until a granulation is formed that masks the bitter taste of the drug. In some instances, e.g. Canadian Patent Application 2,227,314, the molten mixture is cooled to solidify it and then granulated. In WO 98/35656, a solution of the bitter-tasting medicament, a lipid and conventional fillers is filled into suitable forms, the solvent is thereafter removed by freeze-drying or other means and the resulting solid mass removed from the molds to yield discrete dosage units. USP 4,865,851 discloses taste-masking formulations of cefuroxime axetil by an integral coating of a lipid or mixture of lipids.

Regardless of the numerous techniques and pharmaceutical adjuncts known in the art to mask the taste of bitter-tasting medicaments, there remains the need to find an effective technique, adjunct or combination thereof for specific agents. This has been the case with gatifloxacin, particularly with regard to preparations that would be suitable for pediatric administration. Such preparations are provided in accordance with the present invention. It will be appreciated that, while the usefulness of the taste-masked gatifloxacin formed in accordance with the present invention will be emphasized in regard to pediatric medicine, it is likewise useful for preparations

intended for all patients who, as a result of physical challenge or preference, would prefer a liquid preparation. The taste-masked gatifloxacin of the invention is further advantageous in that constituted liquid preparations made therefrom are stable over the normal therapeutic dosage schedule, typically fourteen days.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a form of gatifloxacin having its natural sharply bitter taste sufficiently masked so that it can be effectively utilized in pediatric formulations. Gatifloxacin is formed as a co-precipitate with at least one of stearic acid and palmitic acid in a critical weight ratio. The weight ratio of the two constituents is essential to the advantageous properties of taste-masking and stability of formulations containing it. The present invention further pertains to a process for the preparation of taste-masked gatifloxacin, pharmaceutical formulations containing it and the use thereof in the treatment of a wide variety of infections.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a taste-masked form of the broad spectrum antibacterial gatifloxacin, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

Gatifloxacin is approved for use as a broad spectrum antibacterial therapeutic agent. Gatifloxacin has been shown to be both safe and efficacious in the treatment of infections in hepatically impaired individuals. It has also been shown to be effective against a broad spectrum of microorganisms, including antibiotic-resistant strains of Streptococcus pneumoniae, and to possess excellent overall tolerability.

In accordance with the present invention, it has been found that the characteristic extremely bitter taste of gatifloxacin can be effectively masked by the formation of a crystalline co-precipitate of gatifloxacin and at least one of stearic acid and palmitic acid in a particular weight ratio. Crystalline forms of gatifloxacin

reported in the literature, i.e. the hemihydrate and the sesquihydrate, differ in characteristics and crystalline structure. Although another crystalline form of gatifloxacin could be utilized for the preparation of the subject co-precipitates, the preferred form is the sesquihydrate. The preferred co-precipitant in accordance with the present invention is stearic acid. Crystalline co-precipitates formed in accordance with the present invention have been found to be superior to other recognized mechanisms of combining gatifloxacin with stearic acid, palmitic acid or mixtures thereof in terms of physical characteristics, including stability, and particularly taste-masking. Such other mechanisms include forming a physical mixture, wet or melt granulation and coating of particles of gatifloxacin with the subject fatty acids.

In addition to the fact that the particular mechanism of forming the taste-masked form of gatifloxacin is superior to other methodologies of forming such a composition recognized in the art, it has been found that the use of at least one of stearic acid and palmitic acid to prepare the taste-masked form is advantageous to other art-recognized fatty substances that are often considered at least functionally equivalent thereto by those skilled in the art. Still further, it has been found in accordance with the present invention that a particular narrow weight ratio of gatifloxacin to stearic acid produces optimum parts in comparison to ratios that vary the percentage of the components in favor of one component or the other. While it is known that stearic acid and palmitic acid have been utilized to form taste-masked forms of other therapeutic agents, it is considered unexpected that the form of gatifloxacin formed in accordance with the present invention possesses significant advantages in comparison to similar forms prepared utilizing other fatty substances, by other mechanisms and even wherein the two components are present in different weight ratios.

In accordance with the present invention, there is formed a co-precipitate of gatifloxacin and a fatty acid selected from stearic acid, palmitic acid and mixtures thereof. When the co-precipitate is formed from a mixture of stearic acid and palmitic acid, they are utilized in a weight ratio of from about 1:5 to 5:1, preferably in equal parts by weight. It is preferred to utilize a single fatty acid, most preferably stearic acid, to form the subject co-precipitates. The weight ratio of the fatty acid

component to gatifloxacin utilized in forming the co-precipitates of the present invention varies within a rather narrow range for optimum performance. In general, the weight ratio of gatifloxacin to fatty acid in the subject co-precipitates is from about 1:1.8 to 1:2.3, most preferably about 1:2.1. In regard to only the criteria of taste, formulations prepared from co-precipitates of gatifloxacin and stearic acid in weight ratios of 1:0.7, 1:1 and 1:1.4 have a bitter to bland taste, whereas those prepared with weight ratios of 1:2.8 and 1:3 have an increasingly soapy taste. As noted below, however, while taste is an extremely important characteristic of the subject co-precipitates, it is not the only factor to be considered.

The fact that the subject co-precipitates possess unexpectedly superior properties may be explained by the fact that XRD and NMR studies have shown that the co-precipitate formed from gatifloxacin and fatty acid in a weight ratio of 1:2.1 has a different structure than co-precipitates formed therefrom in weight ratios of 1:1.4 and 1:2.8. While the explanation for this is not certain, it might be expected from the observation that, as the weight ratio of gatifloxacin to fatty acid increases from 1:0.7 to 1:2.1, the solubility of the resulting co-precipitate decreases significantly. The solubility of the co-precipitate is important to its capacity to mask the taste of gatifloxacin since any appreciable dissolution in the mouth may produce a bitter taste in spite of the sweetening and flavoring agents present in the formulation. The capacity to mask the bitter taste of gatifloxacin in the mouth is particularly critical for applications in pediatric medicine.

The co-precipitates of the present invention are advantageous in that, as mentioned above, they are virtually unaffected by factors in the mouth, such as pH and enzymes, that would cause them to dissolve, thereby producing a bitter taste. This is clearly critical since gatifloxacin is very bitter. It has been found, however, that the very small amount of gatifloxacin released in the mouth by dissolution of the co-precipitates of the present invention can be effectively masked by conventional flavoring and sweetening agents. It is a significant and unexpected advantage of the crystalline co-precipitates of the present invention that aqueous suspensions formed therefrom which have been stored under normal conditions for a full dosage cycle, typically up to fourteen days, do not undergo dissolution to any material degree.

This is a distinct advantage because it is commonly recommended by physicians that their patients take the full cycle of treatment with an antibacterial to prevent the possibility of reoccurrence of infection. If the product were to dissociate upon standing over time to an extent such that the flavoring/sweetening agents present was no longer able to mask the inherent bitterness of a bitter therapeutic agent, such as gatifloxacin, the resultant unpleasant taste might result in the patient not completing the prescribed dosage cycle, particularly if that patient is a child.

As noted earlier, in order to be efficacious, a means of masking the bitter taste of a given therapeutic agent must not only be effective in masking the taste and maintain its integrity both in the mouth and over a typical dosage cycle, it must readily release the therapeutic agent in the stomach for absorption. Dissolution studies using the subject gatifloxacin dry preparation for oral suspension formulation at 40 mg/mL in 0.1N hydrochloric acid, pH 1.2, which simulates stomach conditions, indicate 100% release of gatifloxacin in 10 minutes. Further, comparative clinical oral bioavailability studies using the subject gatifloxacin dry preparation for oral suspension at 40 mg/mL have shown that the bioavailability of gatifloxacin from the suspension is 99% relative to a 400-mg tablet.

The co-precipitates of gatifloxacin and fatty acid of the present invention are prepared by initially dissolving the principal ingredients in a suitable solvent, with heat to effect complete dissolution. Preferred solvents to effect solution are low molecular weight alcohols, most preferably ethanol. Generally, gatifloxacin and the fatty acid component are dispersed into the solvent and the resultant dispersion heated to reflux temperature, generally about 80°C, until all solids have completely dissolved. The amount of solvent added to effect dissolution will typically be sufficient to form a solution containing gatifloxacin in a concentration between about 5% and 10% by weight, preferably between about 6.5% and 8% by weight. While a greater amount of solvent could be utilized to form the solutions, these relatively high concentrations of gatifloxacin are preferred not only for obvious reasons of economy, but to maximize crystal growth as well as ease of handling in subsequent operations as will be described below.

Once solution of the principals of the subject co-precipitates is effected, heating is maintained at reflux temperature, i.e. about 80°C with mild agitation, i.e. stirring, for an additional 2 to 3 hours, preferably from about 2 to 2.5 hours. The solution is then slowly cooled to about 18°C with controlled mild agitation to crystallize the co-precipitate. By "slowly cooled" is meant cooling takes place over a period of from about 2.5 to 4 hours. This represents an average cooling rate of from about 0.25°C to 0.4°C per minute. As an optional procedure to overcome the inertia typically characteristic of large-scale processing equipment, the solution may be more rapidly cooled to a temperature not below 45°C, and then slowly cooled as described above.

In the cooling step described above, the onset of crystallization is typically characterized by a mild exotherm of several degrees over a period of from about four to eight minutes before cooling resumes. It is important for optimum crystal growth and subsequent handling of the resultant slurry of the desired crystalline co-precipitate that the rate of agitation, i.e. stirring, of the solution be sufficiently mild so that these events, i.e. the onset of crystallization and the mild exotherm, take place at a temperature of from about 32°C to 35°C. Agitation at an excessive rate will cause both onset of crystallization and mild exotherm to take place as high as 42°C resulting in a slurry that is very difficult to handle and with poor taste characteristics. The manipulation of the various parameters of amount of solvent utilized, cooling rate and rate of stirring within the constraints given above to accomplish the optimum temperature for onset of crystallization and exotherm is considered to be within the purview of those of ordinary skill in the art.

It will be appreciated from the foregoing discussion that the refluxing and slow cooling steps are important in achieving the desired taste-masking properties of the subject crystalline co-precipitates. The slurry of the subject crystalline co-precipitate formed in the cooling step is maintained at from about 15° to 20°C with mild stirring for an additional two to eighteen hours, preferably two to four hours, and vacuum filtered to recover the co-precipitate. The wet cake retained on the filter is oven-dried under vacuum at not more than 30 °C.

In an alternative process, once the solution of the principals of the subject co-precipitates has been formed and heated at reflux as described above, the resultant solution can be directly treated to remove the solvent thereby causing crystallization. This drying treatment may be carried out in an oven, a conventional pan or rotating evaporator, or other similar apparatus. The temperature utilized for solvent removal in an oven is typically between about 40° and 50° C., whereas temperatures in a conventional rotating evaporator may be slightly higher, e.g. from 50° to 60° C. For obvious reasons of economy and the avoidance of solvent disposal issues, the filtration or the drying apparatus is preferably equipped with a means of recovering the solvent to the greatest extent possible so that it may be reused in the process.

The dried co-precipitate is thereafter comminuted to a particle size range that would be suitable to cause the particles to be suspended and periodically redispersed in an aqueous vehicle. In general, an average particle size in the range of 0.5 to 2.0 mm is contemplated, with a particle size range between 0.75 and 1.0 mm being preferred. The comminuting may be carried out on any conventional apparatus equipped with suitable screens to control the size of the resulting particles. It is preferred in accordance with the present invention that the crystalline co-precipitates are initially comminuted to a suitable size as described above and then ground a second time after they have been combined with the excipient materials.

Formulations containing the crystalline co-precipitates of gatifloxacin and a fatty acid are prepared for suspension in an aqueous vehicle by the addition thereto of conventional pharmaceutically acceptable flavoring and sweetening agents. In addition, such formulations may contain pharmaceutically acceptable preservatives, stabilizers, coloring agents, wetting agents and the like. Examples of such agents include: as preservatives, methylparaben, propylparaben and the like; as wetting agents, polyethylene glycol 2000 stearate, sodium lauryl sulfate, polysorbate 80 and the like; as suspending/stabilizing agents, xanthan gum, microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose and the like; as sweeteners, sodium saccharinate, aspartame, xylitol, sucrose and the like; and as flavoring agents, vanilla, caramel sweet tone, guarana and the like. Such agents are typically utilized in the subject compositions in conventional quantities as recommended by the

manufacturer. It is contemplated that such flavoring, sweetening and excipient materials will comprise from about 75 to 90, preferably from about 75 to 85 percent by weight of the final dry formulation.

The formulations containing the subject co-precipitates and the flavoring, sweetening and excipient materials are thoroughly mixed together and, as stated above, preferably again passed through the comminuting device to ensure uniform particle size of the final preparation. They are then packaged in appropriate containers. The container may be oversized to accommodate the appropriate amount of water to form a suspension of the co-precipitates and may further be packaged with a second container containing the requisite quantity of purified water. The formulation and packaging of the subject granulations are such that suspensions formed therefrom by the addition of the recommended volume of water would provide a dosage of 200 mg. of gatifloxacin per 5 mL teaspoonful. This dosage may be modified, for example, for forming a suspension that would be dispensed through a dropper calibrated to provide a predetermined amount of gatifloxacin in a given number of drops or portion of a mL.

It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those of ordinary skill in the art without departing form the scope and spirit of the invention as described above. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the exact description set fuith above, but rather that the claims be construed as encompassing all of the features of patentable novelty that resids in the present invention, including all the features and embodiments that would be treated as equivalents thereof by those skilled in the relevant art. The invention is further described with reference to the following experimental work.

Example 1

Preparation of gatifloxacin-stearic acid crystalline co-precipitate (1:2.1 by weight)

A 3-necked 500-mL reactor equipped with a mechanical agitator (57 mm Teflon paddle impeller), condenser, heating mantle, and cooling bath was charged with 12.776 g of gatifloxacin sesquihydrate, (31.85 mM, 1 eq,) and 27.225 g of stearic acid (95.71 mM, 3.0 eq,) to which was added 240.0 mL of ethanol, 95% USP. The mixture was heated with agitation to obtain a full reflux (~80°C) to dissolve the solids. The resultant solution was heated at reflux with stirring for 2.0 hours. The solution was slowly cooled to 18°C at a cooling-bath rate of 0.25°C per minute with gentle agitation (80-rpm). Total crystallization required about four hours with solids becoming clearly visible when the solution reached 32.5°C. At the onset of crystallization, the batch temperature rose from 32.5°C to 35°C over a period of about five minutes. After this mild exotherm, typical of crystallization procedures, cooling resumed to the desired temperature. The slurry was mixed for a further two hours at 18°C after which the agitation rate was increased to about 300 rpm for about one minute to maximize batch homogeneity and consistency. The slurry was filtered under vacuum on a 7-cm Buchner funnel fitted with Whatman #4 paper filter media. The reactor was rinsed with only re-circulated mother liquor to discharge the solids therefrom. The wet cake was allowed to drain well by vacuum aspiration and then oven-dried using a 30-in Hg vacuum at 30 °C (maximum) until the moisture content by KF attained a value of 1.5%w/w or less. The yield was 37.15 g (36.59 g corrected, 29.78 mM, 93.4 %w/w) of stearic acid-gatifloxacin crystalline co-precipitate with a KF moisture content of 1.5 %w/w.

Example 2

Formulation of gatifloxacin dry preparation for oral suspension

Gatifloxacin dry preparation for oral suspension, 66.1 mg/g.

Ingredient	Amount per kg
Gatifloxacin-Stearic acid Co-precipitate (1:2.1 weight ratio)	216.7 g[a]

Xylitol	168.2 g
Aspartame	99.1 g
Spray Dried Artificial Guarana Flavor	1.9 g
Flavor, Cream de Vanilla Powder (Natural and Artificial) with 5 % Silicon Dioxide	5.9 g
Microcrystalline Cellulose and Sodium Carboxymethylcellulose (Avicel RC-591)	2.8 g
Methylparaben	2.3 g
Propylparaben	0.3 g
Titanium Dioxide	5.4 g
Sucrose	488.4 g

▲ 216.7 g of Gatifloxacin-Stearic acid Co-precipitate is equivalent to 99.1 g of Gatifloxacin, based on 100% purity.

All ingredients were combined and blended for about 10 minutes at about 25 RPM to form a preblend that was then passed through a Fitzmill equipped with a 0.61 mm screen. The milled material was transferred back to the blender and mixed again for about 10 minutes at about 25 RPM. Calculated amounts of the final blend were filled into appropriately sized high-density polypropylene (HDPE) bottles. For example, 63.7 g of the dry preparation was filled into a 200-mL HDPE bottle, which when constituted with 46 mL of water results in 105 mL of suspension containing 40 mg of gatifloxacin per mL. The suspensions were taste-tested over a period of 14 days, which represents a typical dosage cycle for an antibacterial preparation. The results showed that the taste characteristics of the suspensions remained unchanged and satisfactory, indicating that the suspensions were stable over the storage period.

CLAIMS

1. A crystalline co-precipitate of gatifloxacin and a fatty acid selected from the group consisting of stearic acid, palmitic acid and mixtures thereof, wherein the weight ratio of gatifloxacin to said fatty acid is from about 1:1.8 to 1:2.3.

2. A crystalline precipitate in accordance with Claim 1, wherein the weight ratio of gatifloxacin to said fatty acid is about 1:2.1.

3. A crystalline co-precipitate in accordance with Claim 1, wherein said fatty acid is stearic acid.

4. A crystalline co-precipitate in accordance with Claim 2, wherein said fatty acid is stearic acid.

5. A crystalline co-precipitate in accordance with Claim 1, wherein said fatty acid is palmitic acid.

6. A crystalline co-precipitate in accordance with Claim 2, wherein said fatty acid is palmitic acid.

7. A crystalline co-precipitate in accordance with Claim 1, wherein said fatty acid is a mixture of stearic acid and palmitic acid in a weight ratio of from about 1:5 to 5:1.

8. A crystalline co-precipitate in accordance with Claim 7, wherein said fatty acid is a mixture of stearic acid and palmitic acid in about equal parts by weight.

9. A pharmaceutical composition intended for suspension in water for oral administration comprising a crystalline co-precipitate in accordance with Claim 1 and pharmaceutically acceptable excipients.

10. A pharmaceutical composition in accordance with Claim 9, wherein said pharmaceutically acceptable excipients comprise at least one member selected from the group consisting of water-soluble flavoring agents and sweeteners.

11. A pharmaceutical composition in accordance with Claim 9, wherein the fatty acid in the crystalline co-precipitate is stearic acid.

12 A pharmaceutical composition in accordance with Claim 9, wherein the fatty acid in the crystalline co-precipitate is palmitic acid.

13. A pharmaceutical composition in accordance with Claim 9, wherein the fatty acid in the crystalline co-precipitate is a mixture of stearic acid and palmitic acid in a weight ratio of from about 1:5 to 5:1.

14. A method for treating infections in a mammal in need thereof comprising orally administering to the mammal an effective amount of an aqueous suspension of the pharmaceutical composition of Claim 9.

15. A method for treating infections in a mammal in need thereof comprising orally administering to the mammal an effective amount of an aqueous suspension of the pharmaceutical composition of Claim 10.

16. A method for treating infections in a mammal in need thereof comprising orally administering to the mammal an effective amount of an aqueous suspension of the pharmaceutical composition of Claim 11.

17. A method in accordance with Claim 14, wherein said aqueous suspension contains a sufficient amount of said crystalline precipitate to provide a dosage of 200mg. of gatifloxacin in each 5 mL thereof.

18. A process of forming a crystalline co-precipitate of gatifloxacin and a fatty acid selected from the group consisting of stearic acid, palmitic acid and mixtures thereof comprising:

a) dissolving gatifloxacin and said fatty acid in a weight ratio of from about 1:1.8 to 1:2.3 in a suitable solvent with heating to reflux temperature to effect solution thereof;

b) refluxing said solution for from two to three hours with stirring;

c) slowly cooling said solution with stirring to about 18°C over a period of from about 2.5 to 4 hours to precipitate the crystalline co-precipitate of gatifloxacin and said fatty acid;

d) maintaining the resultant slurry of said crystalline co-precipitate to about 15°C to 20°C for an additional two to four hours; and

e) recovering and drying said crystalline co-precipitate.

19. A process in accordance with Claim 18, wherein said solution is formed in step a) with gatifloxacin sesquihydrate.

20. A process in accordance with Claim 18, wherein said fatty acid is stearic acid.

21. A crystalline co-precipitate formed by the process of Claim 18.

22. A crystalline co-precipitate formed by the process of Claim 19.

23. A crystalline co-precipitate formed by the process of Claim 20.

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WO 03/000175 A2

(54) Título: FORMULACIÓN PEDIÁTRICA DE GATIFLOXACINA

(57) Extracto: De acuerdo con la presente invención se provee la gatifloxacina antibacteriana de quinolona con sabor adecuadamente enmascarado, de modo que se pueda utilizar para formulaciones pediátricas. Se ha descubierto que un co-precipitado cristalino de gatifloxacina y uno o ambos de ácido esteárico y ácido palmítico en una estrecha relación de peso enmascaran efectivamente el sabor amargo de la gatifloxacina. El sabor de la gatifloxacina se enmascara efectivamente en la boca y en suspensión acuosa a través de un ciclo completo de posología, típicamente catorce días. Se ha encontrado que la gatifloxacina en los co-precipitados cristalinos en cuestión es fácilmente disponible para absorción desde el estómago.

FORMULACIÓN PEDIÁTRICA DE GATIFLOXACINA

REFERENCIA A APLICACIONES RELACIONADAS

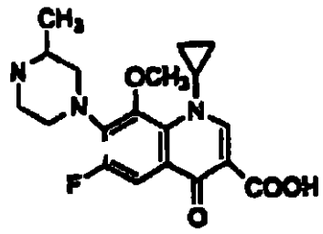
Esta aplicación reivindica el beneficio de la Solicitud Provisional de los Estados Unidos Serie Número 60/299,625 presentada el 20 de junio de 2001.

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con gatifloxacina con sabor adecuadamente enmascarado de modo que pueda utilizarse en formas de posología oral, particularmente para formulaciones pediátricas.

ANTECEDENTES DE LA INVENCIÓN

Gatifloxacina, químicamente ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-(3-metil-1-piperazinil)-4-oxo-3-quinolinacarboxílico, se representa por la siguiente estructura:



Gatifloxacina es un antibacteriano de quinolona de amplio espectro que se divulga y reivindica en la Patente de los Estados Unidos No. 4,980,470, la Patente de los Estados Unidos No. 5,043,450 divulga gatifloxacina aislada como el hemihidrato. La Patente de los Estados Unidos No. 5,880,283 divulga una forma cristalina de sesquihidrato de gatifloxacina que es útil por encima del hemihidrato en la manufactura de productos farmacéuticos. Independientemente de la forma particular de la

gatifloxacina, típica de compuestos de quinolona, tiene un sabor extremadamente amargo.

Se reconoce que los antibacterianos de quinolona, tales como gatifloxacina, tienen aplicación principal en el tratamiento de infecciones en niños. Aquellos antibacterianos que tienen un sabor amargo se encuentran en una desventaja considerable para uso pediátrico puesto que muchas preparaciones pediátricas están en forma líquida para comodidad de administración. Tales agentes terapéuticos sólo pueden administrarse en formas de posología líquidas, incluyendo aquellos constituidos de polvo seco o gránulos, si las formulaciones elaboradas a partir de los mismos tienen por lo menos un sabor aceptable a pacientes pediátricos. Típicamente, tales preparaciones líquidas se hallan disponibles en la forma de polvos o gránulos que se mezclan con agua por un farmacólogo en el momento de dispensarlo para formar una suspensión en un vehículo saborizado. Las partículas finas o gránulos de la sustancia active en tales preparaciones tienen que permanecer suspendidas en el vehículo líquido o re-dispersarse fácilmente en ellas agitando simplemente el envase.

Una desventaja frente a las suspensiones pediátricas como se describe más arriba consiste en que, con el fin de suspenderse fácilmente en un vehículo acuoso, las partículas/gránulos del agente terapéutico son muy finas. La finura de las partículas expone un área muy grande al vehículo acuoso. Como resultado, puede ocurrir la lixiviación del agente terapéutico, particularmente con el transcurso del tiempo. Este fenómeno puede tener lugar independientemente del mecanismo de aglutinamiento utilizado para enmascarar el sabor del agente terapéutico, por ejemplo micro-encapsulación. Además de enmascarar efectivamente el sabor del agente terapéutico, el medio aglutinante o de recubrimiento empleado tiene que mantener la integridad de los gránulos o partículas en la boca porque cualquier solubilización o deslavado apreciable del agente terapéutico por la saliva en la boca anulará potencialmente el sabor aceptable de la

preparación. Además, aunque el medio de enmascarar el sabor del agente terapéutico tiene que mantener su integridad en el vehículo durante un curso normal del tratamiento y en la boca, tiene que liberar fácilmente el agente terapéutico en el estómago para absorción con el fin de que sea eficaz.

En el arte se conocen numerosas técnicas para enmascarar el sabor de agentes terapéuticos amargos. Por ejemplo, la Patente Rumana No. 88836, publicada el 31 de marzo de 1986, divulga un proceso para enmascarar el sabor amargo de la eritromicina que comprende co-precipitación con ácid esteárico en una relación de 1:10 que utiliza acetona como el solvente común a una temperatura que no exceda 40° C. Las tabletas preparadas del producto pueden masticarse o suspenderse en un líquido, típicamente agua, para administración. Otras diferentes técnicas representativas se centran en el enmascaramiento particular de la sustancia del sabor que se mezcla con, se recubre sobre o se combina en otra forma con el medicamento activo de sabor amargo. Ejemplos de tales sustancias incluyen: fosfolípido acídico o lisofosfolípido, EP 0 631 787 B 1; tocoferol polietilenglicol succinato, USP 5,891,469; ciertas resinas de intercambio de iones, WO 01/05431 A1; y ácido embónico, una sal o derivado del mismo, USP 5,808,076. USP 5,622,978 divulga co-precipitados amorfos de dihidropiridinas y un polímero, tal como polivinilpirrolidona, que se administran mediante dispersión en agua. Se afirma que los co-precipitados se forman por técnicas para minimizar la cristalinidad puesto que la cristalinidad tiene un efecto negativo sobre la biodisponibilidad.

Existen en consecuencia un número de enseñanzas de técnicas para recubrir un medicamento de sabor amargo con una sustancia cerosa y luego formar un polvo de ella, típicamente por secamiento de rociado, retiro del solvente asistido por calor, y similares. USP 5,405,617 divulga un método de enmascarar un farmacéutico amargo mezclándolo con estearato estearílico en el estado derretido y congelación por rociado para formar un polvo. La Solicitud Europea EP 0 855 183 A2 divulga un proces similar

en donde un derivado de quinolina y un ácido graso se combinan en un mezclador a una temperatura entre 30° y 140° C y se mezclan hasta que se forme una granulación que enmascara el sabor amargo del fármaco. En algunos casos, por ejemplo, la Solicitud de Patente Canadiense 2,227,314, la mezcla derretida se enfría para solidificarla y luego se granula. En WO 98/35656, una solución del medicamento de sabor amargo, un lípido y cargas convencionales se envasan en formas apropiadas, seguidamente el solvente se retira mediante secamiento por congelamiento u otros medios y la masa sólida resultante se retira de los moldes para proporcionar unidades de posología discretas. USP 4,865,851 divulga formulaciones de enmascaramiento de sabor de cefuroxima axetil por una cubierta integral de un lípido o mezcla de lípidos.

Independientemente de las numerosas técnicas y complementos farmacéuticos conocidos en el arte para enmascarar el sabor de medicamentos de sabor amargo, subsiste la necesidad de encontrar una técnica efectiva, complemento o combinación de los mismos para agentes específicos. Éste ha sido el caso con la gatifloxacina, particularmente con respecto a preparaciones que serían adecuadas para administración pediátrica. Tales preparaciones se proveen de acuerdo con la presente invención. Se apreciará que, aunque la utilidad de la gatifloxacina con sabor enmascarado formada de acuerdo con la presente invención se enfatizará con respecto a la medicina pediátrica, es igualmente útil para preparaciones destinadas a pacientes que, como resultado de exposición física o preferencia, preferirían una preparación líquida. La gatifloxacina con sabor enmascarado de la invención es además ventajosa en el sentido que preparaciones líquidas constituidas elaboradas de ella son estables por encima del programa de posología terapéutica normal, típicamente catorce días.

SUMARIO DE LA INVENCIÓN

De acuerdo con la presente invención, se provee una forma de gatifloxacina que tiene su sabor marcadamente amargo natural suficientemente enmascarado de modo que pueda utilizarse efectivamente en formulaciones pediátricas. La gatifloxacina se forma como un co-precipitado con por lo menos uno de ácido esteárico y ácido palmítico en una relación de peso crítica. La relación de peso de los dos constituyentes es esencial para las propiedades ventajosas del enmascaramiento de sabor y la estabilidad de formulaciones que los contienen. La presente invención concierne además a un proceso para la preparación de gatifloxacina con sabor enmascarado, formulaciones farmacéuticas que la contienen y el uso de las mismas en el tratamiento de una amplia variedad de infecciones.

DESCRIPCIÓN DETALADA DE LA INVENCIÓN

De acuerdo con la presente invención, se provee una forma con sabor enmascarado del antibacteriano de amplio espectro gatifloxacina, ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-(3-metil-1-piperazinil)-4-oxo-3-quinolinacarboxílico.

Gatifloxacina está aprobada para uso como un agente terapéutico antibacteriano de amplio espectro. Se ha comprobado que la gatifloxacina es segura y eficaz en el tratamiento de infecciones en individuos discapacitados hepáticamente. Se ha demostrado asimismo que es efectiva contra un amplio espectro de microorganismos, incluyendo cepas resistentes a los antibióticos de *streptococcus pneumoniae*, y que posee tolerabilidad general excelente.

De acuerdo con la presente invención, se ha descubierto que el sabor característico extremadamente amargo de la gatifloxacina puede enmascararse efectivamente por la formación de un co-precipitado

cristalino de gatifloxacina y por lo menos uno de ácido esteárico y ácido palmítico en una relación de peso particular. Formas cristalinas de gatifloxacina reportadas en la literatura, es decir, el hemihidrato y el sesquihidrato, difieren en características y estructura cristalina. Aunque podría utilizarse otra forma cristalina de gatifloxacina para la preparación de los co-precipitados en cuestión, la forma preferida es el sesquihidrato. El co-precipitante preferido de acuerdo con la presente invención es ácido esteárico. Se ha descubierto que los co-precipitados cristalinos formados de acuerdo con la presente invención son superiores a otros mecanismos reconocidos de combinar gatifloxacina con ácido esteárico, ácido palmítico mezclas de los mismos en términos de características físicas, incluyendo estabilidad, y particularmente enmascaramiento de sabor. Tales otros mecanismos incluyen formar una mezcla física, granulación húmeda o derretida y recubrimiento de partículas de gatifloxacina con los ácidos grasos en cuestión.

Además del hecho que el mecanismo particular de producir la forma con sabor enmascarado de gatifloxacina es superior a otras metodologías de formar tal composición reconocidas en el arte, se ha descubierto que el uso de por lo menos uno de ácido esteárico y ácido palmítico para preparar la forma con sabor enmascarado es ventajosa con respecto a otras sustancias grasas reconocidas por el arte que a menudo se consideran por lo menos funcionalmente equivalentes a ellas por las personas expertas en el arte. Aun más, se ha encontrado de acuerdo con la presente invención que una particular relación estrecha de peso de gatifloxacina a ácido esteárico produce partes óptimas en comparación con relaciones que varían el porcentaje de los componentes a favor de un componente o el otro. Aunque se sabe que el ácido esteárico y el ácido palmítico han sido utilizados para producir formas con sabor enmascarado de otros agentes terapéuticos, se considera inesperado que la forma de gatifloxacina producida de acuerdo con la presente invención posea ventajas significativas en comparación con formas similares preparadas utilizando otras sustancias grasas, por otros

mecanismos e incluso en donde los dos componentes están presentes en diferentes relaciones de peso.

De acuerdo con la presente invención, se forma un co-precipitado de gatifloxacina y un ácido graso seleccionado de ácido esteárico, ácido palmítico y mezclas de los mismos. Cuando el co-precipitado se forma de una mezcla de ácido esteárico y ácido palmítico, éstos se utilizan en una relación de peso de desde alrededor de 1:5 a 5:1, preferiblemente en partes iguales en peso. Se prefiere utilizar un solo ácido graso, muy preferiblemente ácido esteárico, para formar los co-precipitados en cuestión. La relación de peso del componente ácido graso a gatifloxacina utilizada en formar los co-precipitados de la presente invención varía en un rango más bien estrecho de rendimiento óptimo. En general, la relación de peso de gatifloxacina a ácido graso en los co-precipitados en cuestión va desde alrededor de 1:1.8 a 1:2.3, muy preferiblemente alrededor de 1:2.1. Con respecto a únicamente los criterios de sabor, las formulaciones preparadas de co-precipitados de gatifloxacina y ácido esteárico en relaciones de peso de 1:0,7, 1:1 y 1:1.4 tienen un sabor amargo a agradable, mientras que las preparadas con relaciones de peso de 1:2.8 y 1:3 tienen un sabor crecientemente jabonoso. Como se anota más adelante, sin embargo, aunque el sabor es una característica extremadamente importante de los co-precipitados en cuestión, no es el único factor a considerarse.

El hecho de que los co-precipitados en cuestión posean inesperadamente propiedades superiores puede explicarse por el hecho de que estudios con XRD y NMR han mostrado que el co-precipitado formado a partir de la gatifloxacina y ácido graso en una relación de peso de 1:2.1 tiene una estructura diferente de co-precipitados formados a partir de ellos en relaciones de peso de 1:1.4 y 1:2.8. Aunque la explicación de esto no está confirmada, podría deducirse de la observación, a medida la relación de peso de gatifloxacina a ácido graso aumenta de 1:0.7 a 1:2.1, disminuye significativamente la solubilidad del co-precipitado resultante. La

solubilidad del co-precipitado es importante en cuanto a su capacidad de enmascarar el sabor de la gatifloxacina puesto que cualquier disolución apreciable en la boca puede producir un sabor amargo a pesar de los agentes edulcorantes y saborizantes presentes en la formulación. La capacidad de enmascarar el sabor amargo de la gatifloxacina en la boca es particularmente crítica para las aplicaciones en medicina pediátrica.

Los co-precipitados de la presente invención son ventajosos porque, tal como se mencionó arriba, virtualmente no se afectan por factores en la boca, tales como el pH y enzimas, que harían que se disolvieran, produciendo en esa forma un sabor amargo. Esto es evidentemente crítico puesto que la gatifloxacina es muy amarga. Se ha descubierto, sin embargo, que la pequeñísima cantidad de gatifloxacina liberada en la boca por la disolución de los co-precipitados de la presente invención puede enmascararse efectivamente por medio de agentes saborizantes y edulcorantes convencionales. Constituye una ventaja significativa e inesperada de los co-precipitados cristalinos de la presente invención que suspensiones acuosas formadas a partir de ellos, que se han almacenado bajo condiciones normales durante un ciclo completo de posología, típicamente hasta 14 días, no experimentan disolución en ningún grado material.

Ésta es una clara ventaja porque se recomienda comúnmente por los facultativos que sus pacientes tomen el ciclo completo de tratamiento con un antibacteriano para evitar la posibilidad de re-ocurrencia de la infección. Si debido a su almacenamiento prolongado el producto se disociara en una medida tal que los agentes saborizantes/edulcorantes presentes ya no estuvieran en capacidad de enmascarar el amargor inherente de un agente terapéutico amargo, tal como gatifloxacina, el sabor desagradable resultante podría traducirse en que el paciente no concluya el ciclo de posología prescrita, particularmente si el paciente es un niño.

Como se anotó anteriormente, con el fin de ser eficaz, un medio de enmascarar el sabor amargo de un agente terapéutico dado tiene que ser no solamente efectivo en enmascarar el sabor y mantener su integridad tanto en la boca como durante un ciclo de posología típica, sino que tiene que liberar fácilmente el agente terapéutico en el estómago para absorción. Estudios de disolución que usan la preparación seca de la gatifloxacina en cuestión para la formulación de la suspensión oral a 40 mg/mL en 0.1N ácido clorhídrico, pH 1.2, que simula las condiciones estomacales, indican una liberación del 100% de la gatifloxacina en 10 minutos. Además, estudios comparativos de biodisponibilidad oral clínica usando la preparación seca de la gatifloxacina en cuestión para suspensión oral a 40 mg/mL han mostrado que la biodisponibilidad de la gatifloxacina de la suspensión es 99% relativa a una tableta de 400-mg.

Los co-precipitados de gatifloxacina y ácido graso de la presente invención se preparan disolviendo inicialmente los ingredientes principales en un solvente apropiado, con calor para efectuar una disolución completa. Solventes preferidos para realizar la solución son alcoholes de bajo peso molecular, muy preferiblemente etanol. Generalmente, la gatifloxacina y el componente ácido graso se dispersan en el solvente y la dispersión resultante se calienta a temperatura de reflujo, por lo general alrededor de 80° C, hasta que los sólidos se hayan disuelto completamente. La cantidad de solvente agregado para llevar a cabo la disolución será típicamente suficiente para formar una solución que contenga gatifloxacina en una concentración entre alrededor de 5% y 10% en peso, preferiblemente entre alrededor de 6.5% y 8% en peso. Aunque puede utilizarse una cantidad de solvente para formar las soluciones, éstas concentraciones relativamente altas de gatifloxacina se prefieren no sólo por razones obvias de economía, sino que maximizan el crecimiento de cristales así como la facilidad de manejo en operaciones subsiguientes que se describirán más adelante.

Una vez efectuada la solución de los principales de los co-precipitados en cuestión, se mantiene el calentamiento a temperatura de reflujo, es decir, alrededor de 80°C con agitación suave, es decir, agitación, durante 2 a 3 horas más, preferiblemente desde alrededor de 2 a 2.5 horas. Luego la solución se enfría lentamente a alrededor de 18°C con agitación suave controlada para cristalizar el co-precipitado. Por "se enfría lentamente" se da a entender que el enfriamiento tiene lugar durante un período de desde alrededor de 2.5 a 4 horas. Esto representa una tasa promedio de enfriamiento de desde alrededor de 0.25°C a 0.4°C por minuto. Como un procedimiento opcional para superar la inercia típicamente característica de equipo de procesamiento a gran escala, la solución puede enfriarse más rápidamente a una temperatura no por debajo de 45°C, y enfriar luego lentamente como se describe más arriba.

En el paso de enfriamiento ya descrito, la manifestación de la cristalización se caracteriza típicamente por una exoterma suave de varios grados por un periodo de desde alrededor de cuatro a ocho minutos antes que se reinicie el enfriamiento. Es importante para el crecimiento óptimo de los cristales y el manejo subsiguiente de la lechada resultante co-precipitado cristalino deseado que la rata de agitación, es decir, la agitación, de la solución sea suficientemente suave de modo que estos eventos, es decir, la manifestación de la cristalización y la exoterma suave, tengan lugar a una temperatura de desde alrededor de 32°C a 35°C. La agitación a una rata excesiva haría que tanto la manifestación de la cristalización como la exoterma suave tengan lugar a una temperatura tan alta como 42°C lo que resultaría en una lechada que es muy difícil de manejar y con características deficientes de sabor. La manipulación de los distintos parámetros de la cantidad de solvente utilizado, rata de enfriamiento y rata de agitación dentro de las limitaciones dadas más arriba para alcanzar la temperatura óptima para la manifestación de la cristalización y exoterma, se considera que está dentro del alcance de aquellas personas expertas en el arte.

Se apreciará de la discusión anterior que los pasos de reflujo y enfriamiento lento son importantes para el logro de las propiedades deseadas de enmascaramiento de sabor de los co-precipitados cristalinos en cuestión. La lechada del co-precipitado cristalino en cuestión formada en el paso de enfriamiento se mantiene a desde alrededor de 15° a 20°C con agitación suave durante dos a dieciocho horas adicionales, preferiblemente dos a cuatro horas, y se filtra en vacío para recuperar el co-precipitado. La torta húmeda retenida en el filtro se seca en horno bajo vacío a no más de 30 °C.

En un proceso alternativo, una vez se ha formado y calentado a reflujo, como se describe más arriba, la solución de los principales de los co-precipitados en cuestión, la solución resultante puede tratarse directamente para retirar el solvente produciendo de ese modo cristalización. Este tratamiento de secamiento puede llevarse a cabo en un horno, una sartén convencional o evaporador rotatorio, u otro aparato similar. La temperatura utilizada para el retiro del solvente en un horno está típicamente entre alrededor de 40° y 50° C., mientras que las temperaturas en un evaporador rotatorio convencional pueden ser levemente más altas, por ejemplo desde 50° a 60° C. Por razones obvias de economía y prevención de los problemas de disposición final de solventes, el aparato de filtración o secamiento está equipado preferiblemente con un medio de recuperar el solvente en la medida más grande posible de modo que pueda ser reutilizado en el proceso.

El co-precipitado seco se tritura posteriormente en un rango de tamaño de partícula que sería aceptable para hacer que las partículas se suspendan y se re-dispersen periódicamente en un vehículo acuoso. En general, se contempla un tamaño promedio de partícula en el rango de 0.5 a 2.0 mm, prefiriéndose un rango de tamaño de partícula entre 0.75 y 1.0 mm. La reducción a polvo puede llevarse a cabo en cualquier aparato convencional equipado con tamices apropiados para controlar el tamaño de

las partículas resultantes. De acuerdo con la presente invención se prefiere que los co-precipitados cristalinos se desmenucen inicialmente a un tamaño apropiado como se describe más arriba y luego se muelan una segunda vez después de haberse combinado con los materiales excipientes.

Las formulaciones que contienen los co-precipitados cristalinos de gatifloxacina y un ácido graso se preparan para suspensión en un vehículo acuoso mediante la adición a ellos de agentes saborizantes y edulcorantes farmacéuticamente aceptables convencionales. Además, tales formulaciones pueden contener preservantes farmacéuticamente aceptables, estabilizantes, agentes colorantes, agentes humectantes y similares. Ejemplos de tales agentes incluyen: como preservantes, metilparabeno, propilparabeno y similares; como agentes humectantes, polietilen glicol 2000 estearato, lauril sulfato de sodio, polisorbato 80 y similares; como agentes de suspensión/estabilizantes, goma xantana, celulosa microcristalina, carboximetilcelulosa sódica, hidroxipropilcelulosa y similares; como edulcorantes, sacarinato de sodio, aspartame, xilitol, sucrosa y similares; y como agentes saborizantes, vainilla, tono de caramelo dulce, guaraná y similares. Tales agentes se utilizan típicamente en las composiciones en cuestión en cantidades convencionales como las que recomienda el fabricante. Se contempla que tales materiales saborizantes, edulcorante y excipientes comprenderán desde alrededor de 75 a 90, preferiblemente desde alrededor de 75 a 85 por ciento en peso de la formulación final seca.

Las formulaciones que contienen los co-precipitados en cuestión y los materiales saborizantes, edulcorantes y excipientes se mezclan concienzudamente y, como se expuso más arriba, preferiblemente se pasan nuevamente a través del dispositivo desmenuzador para asegurar un tamaño de partícula uniforme de la preparación final. Luego se empacan en envases apropiados. El envase puede ser de mayor tamaño para alojar la cantidad apropiada de agua para formar una suspensión de los co-

precipitados y pueden empacarse además con un segundo envase que contiene la cantidad requerida de agua purificada. La formulación y empacado de las granulaciones en cuestión son tales que las suspensiones formados a partir de ellos por la adición del volumen recomendado de agua proporcionaría una posología de 200 mg de gatifloxacina por una cucharadita de 5 mL. Esta posología puede modificarse, por ejemplo, para formar una suspensión que se dispensaría a través de un cuenta-gotas calibrado para entregar una cantidad pre-determinada de gatifloxacina en un número dado de gotas o porción de un mL.

Se entiende que varias otras incorporaciones y modificaciones en la práctica de la invención serán evidentes a, y pueden elaborarse fácilmente por, aquellas personas de habilidades ordinarias en el arte sin desviarse de la órbita y el espíritu de la invención como se describe anteriormente. En consecuencia, no se pretende que la órbita de las reivindicaciones adjuntas se limite a la descripción exacta enunciada más arriba, sino más bien que las reivindicaciones se interpreten como abarcando todas las características de novedad patentable que se encuentran en la presente invención, incluyendo todas las características e incorporaciones que se tratarían como equivalentes de la misma por aquellas personas expertas en el arte relevante. La invención se describe con mayor detalle con referencia al siguiente trabajo experimental.

Ejemplo 1

Preparación de co-precipitado cristalino de gatifloxacina-ácido esteárico (1:2.1 en peso)

Un reactor de 500-mL de 3 cuellos equipado con un agitador mecánico (impulsor de paletas de teflón de 57 mm), condensador, cubierta de calefacción, y baño de enfriamiento se cargó con 12.776 g de gatifloxacina sesquihidrato, (31.85 mM, 1 eq,) y 27.225 g de ácido esteárico (95.71 mM, 3.0 eq,) a lo cual se agregó 240.0 mL de etanol, 95% USP. La

mezcla se calentó con agitación para obtener un reflujo completo (~80°C) con el fin de disolver los sólidos. La solución resultante se calentó a reflujo con agitación durante 2.0 horas. Se enfrió lentamente la solución a 18°C a una rata de baño de enfriamiento de 0.25°C por minuto con agitación suave (80-rpm). La cristalización total requirió alrededor de cuatro horas haciéndose los sólidos claramente visibles cuando la solución alcanzó 32.5°C. A la aparición de la cristalización, la temperatura del lote subió de 32.5°C a 35°C durante un período de alrededor de cinco minutos. Después de esta exotermia suave, típica de procedimientos de cristalización, se reinició el enfriamiento a la temperatura deseada. La lechada se mezcló durante dos horas más a 18°C luego de lo cual se aumentó la rata de agitación a alrededor de 300 rpm durante alrededor de un minuto para maximizar la homogeneidad del lote y la consistencia. La lechada se filtró bajo vacío en un embudo Buchner de 7-cm Buchner equipado con medios de filtro de papel Whatman #4. Se enjuagó el reactor con agua madre recirculada únicamente para descargar los sólidos de él. Se dejó drenar bien la torta húmeda mediante aspiración de vacío y luego se secó en horno usando un vacío de 30-in Hg a 30 °C (máximo) hasta que el contenido de humedad por KF alcanzó un valor de 1.5% p/p o menos. El rendimiento fue de 37.15 g (36.59 g corregido, 29.78 mM, 93.4 % p/p) de co-precipitado cristalino ácido esteárico-gatifloxacina con un contenido de humedad KF de 1.5 % p/p.

Ejemplo 2

Formulación de preparación seca de gatifloxacina para suspensión oral

Preparación seca de gatifloxacina para suspensión oral, 66.1 mg/g.

Ingrediente	Cantidad por kg
Co-precipitado de gatifloxacina-ácido esteárico (1:2.1 relación de peso)	216.7 g[a]
Xilitol	165.2 g
Aspartame	99.1 0

Sabor de guaraná artificial secado por aspersión	1.98
Sabor, polvo de crema de vainilla (natural y artificial) con 5 % dióxido de silicio	6.9 6
Celulosa microcristalina y carboximetilcelulosa sódica (Avicel RC-591)	2.6 g
Metilparabeno	2.3[*]g
Propilparabeno	0.3 g
Dióxido de titanio	5.4 g
Sucrosa	499.4 g

* 216.7 g de co-precipitado de gatifloxacina-ácido esteárico equivalen a 66.1 g de gatifloxacina, basado en una pureza del 100%.

Todos los ingredientes se combinaron y mezclaron durante alrededor de 10 minutos a alrededor de 25 RPM para formar una pre-mezcla que se pasó entonces por un pulverizador Fitzmill equipado con una criba de à 0.61 mm. El material molido se transfirió otra vez al mezclador y se mezuló nuevamente durante alrededor de 10 minutos a alrededor de 25 RPM. Cantidades calculadas de la mezcla final se envasaron en frascos de polietileno de alta densidad (HDPE), apropiadamente dimensionados. Por ejemplo, 63.7 g de la preparación seca se envasaron en un frasco HDPE de 200-mL, que cuando se constituye con 46 mL de agua resulta en 105 mL de suspensión que contiene 40 mg de gatifloxacina por mL. Las suspensiones se probaron en cuanto a sabor durante un período de 14 días, lo cual representa un ciclo de posología típica para una preparación antibacteriana. Los resultados mostraron que las características de sabor de las suspensiones permanecieron inmodificadas y satisfactorias, indicando que las suspensiones eran estable durante el período de almacenamiento.

REIVINDICACIONES

1. Un co-precipitado cristalino de gatifloxacina y un ácido graso seleccionado del grupo conformado por ácido esteárico, ácido palmítico y mezclas de los mismos, en donde la relación de peso de gatifloxacina a dicho ácido graso es desde alrededor de 1:1.8 a 1:2.3.

2. Un precipitado cristalino de acuerdo con Reivindicación 1, en donde la relación de peso de gatifloxacina a dicho ácido graso es de alrededor de 1:2.1.

3. Un co-precipitado cristalino de acuerdo con Reivindicación 1, en donde dicho ácido graso es ácido esteárico.

4. Un co-precipitado cristalino de acuerdo con Reivindicación 2, en donde dicho ácido graso es ácido esteárico.

5. Un co-precipitado cristalino de acuerdo con Reivindicación 1, en donde dicho ácido graso es ácido palmítico.

6. Un co-precipitado cristalino de acuerdo con Reivindicación 2, en donde dicho ácido graso es ácido palmítico.

7. Un co-precipitado cristalino de acuerdo con Reivindicación 1, en donde dicho ácido graso es una mezcla de ácido esteárico y ácido palmítico in una relación de peso de desde alrededor de 1:5 a 5:1.

8. Un co-precipitado cristalino de acuerdo con Reivindicación 7, en donde dicho ácido graso es una mezcla de ácido esteárico y ácido palmítico en partes aproximadamente iguales en peso.

9. Una composición farmacéutica prevista para suspensión en agua para administración oral que comprende un co-precipitado cristalino de acuerdo con Reivindicación 1 y excipientes farmacéuticamente aceptables.

10. Una composición farmacéutica de acuerdo con Reivindicación 9, en donde dichos excipientes farmacéuticamente aceptables comprenden por lo menos un número seleccionado del grupo conformado por agentes saborizantes solubles en agua y edulcorantes.

11. Una composición farmacéutica de acuerdo con Reivindicación 9, en donde el ácido graso en el co-precipitado cristalino es ácido esteárico.

12. Una composición farmacéutica de acuerdo con Reivindicación 9, en donde el ácido graso en el co-precipitado cristalino es ácido palmítico.

13. Una composición farmacéutica de acuerdo con Reivindicación 9, en donde el ácido graso en el co-precipitado cristalino es una mezcla de ácido esteárico y ácido palmítico in una relación de peso de desde alrededor de 1:5 a 5:1.

14. Un método para tratar infecciones en un mamífero necesitado que comprende administrar oralmente al mamífero una cantidad efectiva de una suspensión acuosa de la composición farmacéutica de Reivindicación 9.

15. Un método para tratar infecciones en un mamífero necesitado que comprende administrar oralmente al mamífero una cantidad efectiva de una suspensión acuosa de la composición farmacéutica de Reivindicación 10.

16. Un método para tratar infecciones en un mamífero necesitado que comprende administrar oralmente al mamífero una cantidad efectiva de

una suspensión acuosa de la composición farmacéutica de Reivindicación 11.

17. Un método de acuerdo con Reivindicación 14, en donde dicha suspensión acuosa contiene una cantidad suficiente de dicho precipitado cristalino para proveer una posología de 200 mg de gatifloxacina en cada 5 mL de la misma.

18. Un proceso de formar un co-precipitado cristalino de gatifloxacina y un ácido graso seleccionado del grupo conformado por ácido esteárico, ácido palmítico y mezclas de los mismos que comprende:

a) disolver la gatifloxacina y dicho ácido graso en una relación de peso de desde alrededor de 1:1.8 a 1:2.3 en un solvente apropiado con calentamiento a temperatura de reflujo para efectuar la solución de la misma;

b) hacer refluir dicha solución durante desde dos a tres horas con agitación;

c) enfriar lentamente dicha solución con agitación a alrededor de 18°C durante un periodo de desde alrededor de 2.5 a 4 horas para precipitar el co-precipitado cristalino de gatifloxacina y dicho ácido graso;

d) mantener la lechada resultante de dicho co-precipitado cristalino a alrededor de 15°C a 20°C durante un período adicional de dos a cuatro horas; y

e) recuperar y secar dicho co-precipitado cristalino.

19. Un proceso de acuerdo con Reivindicación 18, en donde dicha solución se forma en paso a) con sesquihidrato de gatifloxacina.

20. Un proceso de acuerdo con Reivindicación 18, en donde dicho ácido graso es ácido esteárico,

21. Un co-precipitado cristalino formado por el proceso de Reivindicación 18.

22. Un co-precipitado cristalino formado por el proceso de Reivindicación 19.

23. Un co-precipitado cristalino formado por el proceso de Reivindicación 20.

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PCT/US02/14596

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
DAVID M. MORSE
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

JAN 03 2003
Docketed Item
Due Date 4/2/03
Attorney

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference TN22	Date of Mailing *(day/month/year)* 03 JAN 2003 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/14596	International filing date *(day/month/year)* 10 May 2002 (10.05.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
   1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of *(an)* additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminder

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Emily Bernhardt Telephone No. (703) 308-1235

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference TN22	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/14596	International filing date (*day/month/year*) 10 May 2002 (10.05.2002)	(Earliest) Priority Date (*day/month/year*) 20 June 2001 (20.06.2001)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 31 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☐ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/14596

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/496; C07D 401/10.
US CL : 514/253.08; 544/363.
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)
U.S. : 514/253.08; 544/363.

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)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,980,470 A (MASUZAWA et al.) 25 December 1990.	1-23
A	Chem. abstr., Vol.106, No.8, 23 February 1987 (Columbus,OH,USA), page 377, column 1, the abstract No.55949d, BALOESCU et al. "Erythromycin propionate tablets for pediatric use" RO 88,836 (31 March 1986).	1-23

☐ Further documents are listed in the continuation of Box C. ☐ 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 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
09 August 2002 (09.08.2002)	03 JAN 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Emily Bernhardt Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-30 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequences if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequences with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

I. Certification under 37 CFR 1.10 (if applicable)

EM235841665US	13-01-03
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

[signature]	Warren K. Velles
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☐ New International Application

TITLE		Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was not made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).*

application no.		filed on	
application no.		filed on	

D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.

E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages [ ] and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☒ Other (please specify): PCT Demand for International Preliminary Examination; PCT Demand Fee Calculation Sheet

The person signing this form is the:		
	☐ Applicant	Warren K. Velles
	☒ Attorney/Agent (Reg. No.) 33,810	Typed name of signer
	☐ Common Representative	[signature]
		Signature

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference TN22
International application No. PCT/US02/14598	International filing date *(day/month/year)* 10 May 2002 (10-05-02)	(Earliest) Priority date *(day/month/year)* 20 June 2001 (20-06-01)
Title of invention Pediatric Formulation of Gatifloxacin		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. 609-252-3414
BRISTOL-MYERS SQUIBB COMPANY PO Box 4000 Princeton, New Jersey 08543-4000 United States of America	Facsimile No. 609-252-4526
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

30

Box No. III AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.

☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official The address must include postal code and name of country.)*

VOLLES, Warren K.
Bristol-Myers Squibb Company
PO Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.
203-677-6997

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office
33,810

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed.

the description
☐ as originally filed
☐ as amended under Article 34

the claims
☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.
☒ which is the language of a translation furnished for the purposes of international search.
☒ which is the language of publication of the international application.
☒ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

39

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

W. Warren K. Metlitz, Agent

Warren K. Metlitz

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No.	PCT/US02/14596
Applicant's or agent's file reference	TN22

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant
BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	750.00	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	137.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	887.00	
	TOTAL	

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ US

- [X] Authorization to charge the total fees indicated above.
- [X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19-3880

Date: January 13, 2003

Name: Warren K. Volles

Signature: Warren K. Volles

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* TN22

Box No. I TITLE OF INVENTION

Pediatric Formulation of Gatifloxacin

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BRISTOL-MYERS SQUIBB COMPANY
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.
609-252-4338

Facsimile No.
609-252-4526

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RAGHAVAN, Krishnaswamy S.
3 Hickory Court
Cranbury, New Jersey 08512
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MORSE, David M.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.
203-677-6997

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office
25,742

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RANADIVE, Sunanda A.
24 Agate Road
East Brunswick, New Jersey 08816
United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BEMBENEK, Kenneth S.
F - 12 Lincoln Lane
Dayton, New Jersey 08810
United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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BENKERROUR, Loutfy
18, Rue Tiphaine
75015 Paris
France

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TROGNON, Veronique
9 Chemin du Guenoll
44420 La Turballe
France

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

(If none of the following boxes is used, these sheets should not be included in the request.)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CORRAO, Richard G.
One East Dickens Court
Jackson, New Jersey 08527
United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ESPOSITO, Luigi
29 Lexington Road
Howell, New Jersey 07731
United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Cote d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☒	AE	United Arab Emirates	☒	GM	Gambia	☒	NZ	New Zealand
☒	AG	Antigua and Barbuda	☒	HR	Croatia	☒	OM	Oman
☒	AL	Albania	☒	HU	Hungary	☒	PH	Philippines
☒	AM	Armenia	☒	ID	Indonesia	☒	PL	Poland
☒	AT	Austria	☒	IL	Israel	☒	PT	Portugal
☒	AU	Australia	☒	IN	India	☒	RO	Romania
☒	AZ	Azerbaijan	☒	IS	Iceland	☒	RU	Russian Federation
☒	BA	Bosnia and Herzegovina	☒	JP	Japan			
☒	BB	Barbados	☒	KE	Kenya	☒	SD	Sudan
☒	BG	Bulgaria	☒	KG	Kyrgyzstan	☒	SE	Sweden
☒	BR	Brazil	☒	KP	Democratic People's Republic of Korea	☒	SG	Singapore
☒	BY	Belarus				☒	SI	Slovenia
☒	BZ	Belize	☒	KR	Republic of Korea	☒	SK	Slovakia
☒	CA	Canada	☒	KZ	Kazakhstan	☒	SL	Sierra Leone
☒	CH & LI	Switzerland and Liechtenstein	☒	LC	Saint Lucia	☒	TJ	Tajikistan
☒	CN	China	☒	LK	Sri Lanka	☒	TM	Turkmenistan
☒	CO	Colombia	☒	LR	Liberia	☒	TN	Tunisia
☒	CR	Costa Rica	☒	LS	Lesotho	☒	TR	Turkey
☒	CU	Cuba	☒	LT	Lithuania	☒	TT	Trinidad and Tobago
☒	CZ	Czech Republic	☒	LU	Luxembourg			
☒	DE	Germany	☒	LV	Latvia	☒	TZ	United Republic of Tanzania
☒	DK	Denmark	☒	MA	Morocco	☒	UA	Ukraine
☒	DM	Dominica	☒	MD	Republic of Moldova	☒	UG	Uganda
☒	DZ	Algeria				☐	US	United States of America
☒	EC	Ecuador	☒	MG	Madagascar			
☒	EE	Estonia	☒	MK	The former Yugoslav Republic of Macedonia	☒	UZ	Uzbekistan
☒	ES	Spain				☒	VN	Viet Nam
☒	FI	Finland	☒	MN	Mongolia	☒	YU	Yugoslavia
☒	GB	United Kingdom	☒	MW	Malawi	☒	ZA	South Africa
☒	GD	Grenada	☒	MX	Mexico	☒	ZM	Zambia
☒	GE	Georgia	☒	MZ	Mozambique	☒	ZW	Zimbabwe
☒	GH	Ghana	☒	NO	Norway			

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ ..... ☐ ..... ☐ .....

☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 20 June 2001 (20-06-01)	60/299,625	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* .....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ US.....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration): Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

(a) the following number of sheets in paper form:			
request (including declaration sheets)	:	6	
description (excluding sequence listing part)	:	12	
claims	:	3	
abstract	:	1	
drawings	:	0	
Sub-total number of sheets	:	22	
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:		
Total number of sheets	:	22	

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801 (a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801 (a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	of items
1. ☒ fee calculation sheet	: 1
2. ☒ original separate power of attorney	: 1
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
10. ☐ other *(specify)*:	:

Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

David M. Morse Agent

David M. Morse

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: TN22

Applicant: BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE ..... 240.00 T

2. SEARCH FEE ..... 700.00 S

International search to be carried out by: US

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets
Where item (b) of Box No. IX does not apply, enter Total number of sheets: 21

b1 first 30 sheets 407.00 b1

b2 0 (number of sheets) x 9.00 (fee per sheet) = 0.00 b2

b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ b3

Add amounts entered at b1, b2 and b3 and enter total at B ... 407.00 B

Designation Fees

The international application contains 109 designations.

5 (number of designation fees payable *(maximum 5)*) x 88.00 (amount of designation fee) = 440.00 D

Add amounts entered at B and D and enter total at I ..... 847.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* ..... 15.00 P

5. TOTAL FEES PAYABLE ..... 1,862.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge ☐ postal money order ☐ cash ☐ coupons

☐ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ US

☒ Authorization to charge the total fees indicated above.

Deposit Account No.: 18-3880

☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Date: May 10, 2002

Name: David M. Morse

☐ Authorization to charge the fee for priority document.

Signature: David M. Morse

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/299,625	06/20/2001		150	10022 PSP			

CONFIRMATION NO. 3863

23914
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

RECEIVED
U.S. Patent Law
SEP 10 2001
Docketed Item
Due Date
Attorney D.M.

FILING RECEIPT

"OC000000006931123"

Date Mailed: 09/07/2001

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Krishnaswamy Raghavan, Cranbury, NJ;
Sunanda A. Ranadive, East Brunswick, NJ;
Kenneth S. Bembenek, Dayton, NJ;
Loutfy Benkerrour, Paris, FRANCE;
Veronique Trognon, La Turballe, FRANCE;
Richard G. Corrao, Jackson, NJ;
Luigi Esposito, Howell, NJ;

If Required, Foreign Filing License Granted 09/07/2001

Projected Publication Date: N/A

Non-Publication Request: No

Early Publication Request: No

Title

Pediatric formulation of gatifloxacin

Data entry by : GOITOM, AYIDA   Team : OIPE   Date: 09/07/2001

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15 .

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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PLEASE NOTE the following information about the Filing Receipt:

- The articles such as "a," "an" and "the" are not included as the first words in the title of an application. They are considered to be unnecessary to the understanding of the title.
- The words "new," "improved," "improvements in" or "relating to" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 500 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
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Assistant Commissioner for Patents
Office of Initial Patent Examination
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Washington, DC 20231

AS: 92.518

51

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARIA CASTALDO

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARIA CASTALDO, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

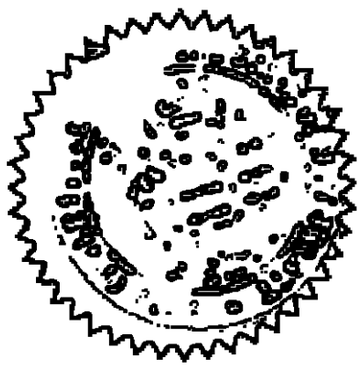
6. THE 31ST DAY OF OCTOBER 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A185325

9. SEAL/STAMP:

10. SIGNATURE



TN0022-60/299,625 – CO

AFFIDAVIT

I, Stephen B. Davis, Senior Patent Counsel, Patent Department, BRISTOL-MYERS SQUIBB COMPANY, do hereby certify that this is a notarized true and accurate assignment signed by the inventors.

Stephen B. Davis
Senior Patent Counsel

STATE OF NEW JERSEY)
)
COUNTY OF MERCER)

Subscribed and sworn to before me this

28 day of Oct., 2003

Maria Castaldo
Notary Public of New Jersey
My commission expires October 6, 2008

SEAL

532

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JUNE 19, 2002

PTAS

BRISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
P.O. BOX 4000
PATENT DEPARTMENT
PRINCETON, NJ 08543-4000

700014084A

700014084A

UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 06/18/2002

REEL/FRAME: 012810/0400
NUMBER OF PAGES: 8

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
RAGHAVEN, KRISHNASWAMY
DOC DATE: 07/24/2001

ASSIGNOR:
RANADIVE, SUNANDA A.
DOC DATE: 07/24/2001

ASSIGNOR:
REMBENER, KENNETH S.
DOC DATE: 07/24/2001

ASSIGNOR:
BENKERROUR, LOUTFY
DOC DATE: 07/10/2001

ASSIGNOR:
TROGNON, VERONIQUE
DOC DATE: 07/10/2001

ASSIGNOR:
CORRAO, RICHARD G.
DOC DATE: 07/24/2001

ASSIGNOR:
ESPOSITO, LUIGI
DOC DATE: 07/24/2001

012810/0400 PAGE 2

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 60299625
PATENT NUMBER:

FILING DATE: 06/20/2001
ISSUE DATE:

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

FORM PTO-1595 (Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Krishnaswamy Raghavan, Sunanda A. Ranadive, Kenneth S. Bembenek, Laurent Bonkoungou, Veronique Tregnan, Richard G. Cerrao, Luigi Esposito

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: Bristol-Myers Squibb Company
Internal Address:
Street Address: Lawrenceville-Princeton Road
City: Princeton State: NJ ZIP: 08543-4000
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: 7/24/01, 7/24/01, 7/24/01, 7/10/01, 7/10/01, 7/24/01, 7/24/01

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
USSN 60/299,928 filed June 20, 2001

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Stephen B. Davis
Internal Address: Bristol-Myers Squibb Company
Patent Department
Street Address: P.O. Box 4000
City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40
☐ Enclosed
☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
19-3880 (in the name of Bristol-Myers Squibb Company)
(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David M. Morse — [signature] — 6/18/2002
Name of Person Signing — Signature — Date
Reg. No. 35,742

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Total number of pages including cover sheet, attachments, and document: 6

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Patent and Trademark Office

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Krishnaswamy Raghavan, Sunanda A. Ranadive, Kenneth S. Bembenek, Loutfy Benkerrour, Veronique Trognon, Richard G. Corrao, Luigi Esposito

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: Bristol-Myers Squibb Company
Internal Address: _____
Street Address: Lawrenceville-Princeton Road
City: Princeton State: NJ ZIP: 08543-4000
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____
Execution Date: 7/24/01, 7/24/01, 7/24/01, 7/10/01, 7/10/01, 7/24/01, 7/24/01

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: _____
A. Patent Application No.(s)
USSN 60/299,825 filed June 20, 2001
B. Patent No.(s)
Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Stephen B. Davis
Internal Address: Bristol-Myers Squibb Company
Patent Department
Street Address: P.O. Box 4000
City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40
☐ Enclosed
☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
18-3880 (in the name of Bristol-Myers Squibb Company)
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David M. Morse — Name of Person Signing
Reg. No. 25,742
David M Morse — Signature
6/18/2002 — Date

☐ Certificate of mailing on reverse side
Total number of pages including cover sheet, attachments, and document: 8

Mail documents to be recorded with required cover sheet information to:
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Washington, D.C. 20231

Worldwide
Case TN22 PSP

ASSIGNMENT

We,

Krishnaswamy Raghavan	residing at	3 Hickory Court Cranbury, New Jersey 08512 United States of America
Sunanda A. Ranadive	residing at	24 Agate Road East Brunswick, New Jersey 08816 United States of America
Kenneth S. Bembenek	residing at	F - 12 Lincoln Lane Dayton, New Jersey 08810 United States of America
Loutfy Benkerrour	residing at	18, Rue Tiphaine Paris 75015 France
Veronique Trognon	residing at	9 Chemin du Guenoll La Turballe 44420 France
Richard G. Corrao	residing at	One East Dickens Court Jackson, New Jersey 08527 United States of America
Luigi Esposito	residing at	29 Lexington Road Howell, New Jersey 07731 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any International convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Pediatric Formulation of Gatifloxacin

invented by us and described in the provisional United States patent application

Application No. 60/299,625, filed June 20, 2001

Including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 24th day of July, 2001 by
Krishnaswamy Raghavan

Signed this 24th day of July, 2001 by
Sunanda A. Ranadive

Signed this 24th day of July, 2001 by
Kenneth S. Bambenek

Signed this 10th day of July, 2001 by
Loutfy Benkerrour

Signed this 10th day of July, 2001 by
Veronique Tuphem

Signed this 24th day of July, 2001 by
Richard G. Corrao

Signed this 24th day of July, 2001 by
Luigi Esposito

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 24th day of July, 2001, before me came Krishnaswamy Raghavan, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

[SEAL]

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 24th day of July, 2001, before me came Sunanda A. Ranadive, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

YVONNE SMITH
Notary Public Of New Jersey
My Commission Expires June 13, 2006

[SEAL]

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 24th day of July, 2001, before me came Kenneth S. Bembenek, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

[illegible]
Notary Public of New Jersey
My Commission Expires June 11, 2005

[SEAL]

COUNTRY OF France)
) ss.
PROVINCE OF)
LOIRE-ATLANTIQUE

On the 10TH day of JULY, 2001, before me came Loutfy Benkerrour, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

LUCIEN CHAPEL
Notary Public (Printed Name)

Me Lucien CHAPEL - Notaire Associé
44500 LA BAULE

[SEAL]

COUNTRY OF France)
) ss.
PROVINCE OF LOIRE-ATLANTIQUE)

On the 10TH day of JULY, 2001, before me came Veronique Trognon, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public (Signature)

LUCIEN CHAPEL
Notary Public (Printed Name)

Me Lucien CHAPEL - Notaire Associé 44500 LA BAULE

[SEAL]

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 24th day of July, 2001, before me came Richard G. Conrad, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

YVONNE ZIRRITH
Notary Public Of New Jersey
My Commission Expires June 13, 2006

[SEAL]

Worldwide
Case TN22 PSP

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 24th day of July, 2001, before me came Luigi Esposito, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Notary Public

YVONNE ZIOBRO
Notary Public Of New Jersey
My Commission Expires June 13, 2006

[SEAL]

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
Dibujos de ser estos pertinentes.	( )	( )
Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
- Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

SUPERINTENDENCIA DE COMERCIO
Radicación: [illegible] Folios: 54
Fecha [illegible]
Tramite : [illegible]
Dependencia: [illegible]

666

No de Radicación: 03-107426

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+-------------------------------------------------------------+
|ACCION: Consultar Siguiente Anterior Ir al detalle Primero ... |
|Seleccionar un(os) Registros                                 |
|-------------------------------------------------------------|
|SUPERINDUSTRIA Y COMERCIO                SISTEMA DE REGISTRO |
|                          Fecha 07/01/2004                   |
|-------------------------------------------------------------|
|              MANTENIMIENTO DE PROTOCOLOS                    |
|Numero : 19358                                               |
|Fecha  : 07/05/1999                                          |
|Conferido: BRISTOL-MYERS SQUIBB COMPANY                      |
|                                                             |
|Pais   : US   ESTADOS UNIDOS DE AMERICA                      |
|Ciudad :  82  PRINCETON, NEW JERSEY                          |
|Represent: S     Sustituir : S     Desistir : S              |
|No. Radicacion : 99  28346   Clase:  0  Secv:  0  Seac:  0   |
|-------------------------------------------------------------|
|scncia Codigo Ctr              Nombre                        |
| 1    340  A   CASTRO DUQUE RAMIRO                          |
| 2   3002      GOMEZ MEJIA HECTOR                            |
|                                                             |
|              Encontrados (1/1) registro(s)                  |
+-------------------------------------------------------------+
```

Industria y Comercio
SUPERINTENDENCIA

Folio: 86

2020
Bogotá DC

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL – MYERS SQUIBB COMPANY

REFERENCIA:	Radicación No.	03-107426
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	164
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 04 FEB. 2004

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202054

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