

FIG. 2

US 6,652,881 B2

1

**FENOFIBRATE PHARMACEUTICAL
COMPOSITION HAVING HIGH
BIOAVAILABILITY**

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/126,875 filed Apr. 22, 2002; which is a continuation of U.S. application Ser. No. 10/078,500 filed Feb. 21, 2002; which is a continuation of U.S. application Ser. No. 09/899,026 filed Jul. 6, 2001; which is a continuation of U.S. application Ser. No. 09/572,330 filed May 18, 2000, issued as U.S. Pat. No. 6,277,405; which is a continuation of U.S. application Ser. No. 09/005,128 filed Jan. 9, 1998, issued as U.S. Pat. No. 6,074,670; which claims priority to French Application No. 97 00 479 filed Jan. 17, 1997.

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to its poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia); product dissolution

2

kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits: 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate solution is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxyethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight, based on the weight of the active ingredient, which, bearing in mind the presence of the inert pellets of a large size (about 700 µm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this document is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained

US 6,652,881 B2

3

in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuehiki et al., *Yakuzaigaku*, 44 No. 1, 31-37 (1984) describes such a technique for preparing solid dispersions using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

WO-A-96 01621 further discloses a sustained release composition, comprising an inert core (silica in all examples) coated with a layer which contains the active ingredient in admixture with a hydrophilic polymer, the weight ratio active ingredient/polymer being comprised between 10/1 and 1/2 and the weight ratio active ingredient/inert core being comprised between 5/1 and 1/2, with an outer layer to impart the sustained release property. These compositions can be compressed. The hydrophilic polymer can be polyvinylpyrrolidone. This document also discloses a process for preparing said composition; for example in a fluidized-bed granulator one will spray a dispersion of active ingredient in a polymer solution onto the inert cores. This document solely relates to sustained release compositions, the technical problem to be solved being the compression, without damages, of the outer layer imparting the sustained release property.

Nevertheless, nothing in the state of the art teaches nor suggest the present invention.

SUMMARY OF THE INVENTION

Thus, the present invention provides an immediate-release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 20 μm , a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 20% by weight of (a); and

(b) optionally one or several outer phase(s) or layer(s). In one embodiment, a surfactant is present with the active ingredient and the hydrophilic polymer.

The invention also provides a composition comprising fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

A method for preparing a pharmaceutical composition is also provided, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20 μm , in a solution of hydrophilic polymer and, optionally surfactant;

(b) applying the suspension from step (a) to an inert hydrosoluble carrier;

(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

4

Step (b) is preferably carried out in a fluidized-bed granulator.

The method can comprise a step in which products obtained from step (b) or (c) are compressed, with or without additional excipients.

The invention also provides a suspension of fenofibrate in micronized form having a size less than 10 μm , in a solution of hydrophilic polymer and, optionally, surfactant.

The invention will be described in more detail in the description which follows, with reference to the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of a comparative study of the dissolution profile of a composition according to the invention, compared to that of Lipanthyl® 200M;

FIG. 2 is a graph illustrating a comparative study of the dissolution profile of a composition according to the invention and that of pharmaceutical products commercially available on the German market.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The expression "in micronized form" in this invention means a substance in a particulate form, the dimensions of the particles being less than or equal to about 20 μm .

Advantageously, this dimension is less than or equal to 10 μm .

In the framework of this invention, the expression "inert hydrosoluble carrier" means any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium. Examples of such excipients are derivatives of sugars, such as lactose, saccharose, hydrolyzed starch (malto-dextrine), etc. Mixture are also suitable. The individual particle size of the inert hydrosoluble carrier can be, for example, between 50 and 500 microns.

The expression "hydrophilic polymer" in the invention should be taken to mean any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel. Examples of such polymers are polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc. Polymer blends are also suitable.

The preferred hydrophilic polymer is polyvinylpyrrolidone (PVP). The PVP used in this invention has, for example, a molecular weight comprised between 10,000 and 100,000, preferably for example between 20,000 and 55,000.

The term "surfactant" is used in its conventional sense in this invention. Any surfactant is suitable, whether it be amphoteric, non-ionic, cationic or anionic. Examples of such surfactants are: sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearic alcohol, cetostearyl alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty

US 6,652,881 B2

5

acid glycerides, poloxamer®, etc. Mixtures of surfactants are also suitable.

The preferred surfactant is sodium laurylsulfate, which can be co-micronized with fenofibrate.

The compositions according to the invention can additionally contain any excipient conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as binders, fillers, pigments, disintegrating agents, lubricants, wetting agents, buffers, etc. As examples, excipients able to be used in this invention we can cite: microcrystalline cellulose, lactose, starch, colloidal silica, talc, glycerol esters, sodium stearyl fumarate, titanium dioxide, magnesium stearate, stearic acid, cross-linked polyvinyl pyrrolidone (AC DI SOL®), carboxymethyl starch (Exploitab®, Primoje®), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc.

Here, the expression "outer phase or layer" should be taken to mean any coating on the element (a) with the active ingredient (forming a "core"). Indeed, it can be useful to have available one or several phase(s) or layer(s) on top of the coated core. The invention thus covers a single core with one layer, but also several cores in a phase, as is the case of tablets which are formed from "cores" mixed with a phase.

This outer layer comprises conventional excipients.

It is also possible to provide a layer comprising additives, for the manufacture of tablets. In this embodiment, the outer layer comprises a disintegration agent and, for example, a lubricant; the thus covered and mixed granules can then be readily compressed and easily disintegrate in water.

The compositions according to the invention comprise, in general, based on the total composition weight excluding the outer phase or layer, an inert hydro-soluble carrier making up from 10 to 80% by weight, preferably 20 to 50% by weight, the fenofibrate representing from 5 to 50% by weight, preferably from 20 to 45% by weight, the hydrophilic polymer representing from 20 to 60% by weight, preferably 25 to 45% by weight, the surfactant making up from 0 to 10% by weight, preferably 0.1 to 3% by weight.

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

The hydrophilic polymer represents preferably more than 25% by weight, based on the weight of (a).

The weight ratio of fenofibrate/hydrophilic polymer can for example be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1.

When a surfactant is employed, the weight ratio surfactant/hydrophilic polymer can be comprised for example between 1/500 and 1/10, preferably, for example, between 1/100 and 5/100.

In one embodiment, the composition according to the invention takes the form of tablets.

This tablet preferably results from the compression of elements (a) (under the form of granules) together with an outer phase.

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

6

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

The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert core.

When a surfactant is present, the active ingredient can be co-micronized with the surfactant. One will then use with advantage the teachings of EP-A-0330532.

The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bio-availability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophilic polymer and, optionally, a surfactant.

The fluidized-bed granulation technique is widely used in the pharmaceutical industry for preparing capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient+excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art and reference should be made to standard works such as for example "Die Tablette", by Ritschel, Ed. Cantor Aulendorf, pages 211-212.

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

The compositions according to the invention can also be prepared by other methods, for example by spraying a solution of the micronized active ingredient onto the hydro-soluble inert carrier.

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

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

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

The significant starting product is the suspension of the active ingredient. This suspension is prepared by putting the micronized active ingredient into suspension in a solution comprising the hydrophilic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent (beaker+magnetic or vane stirrer). Next, the hydrophilic polymer

US 6,652,881 B2

7

(PVP) is dispersed, while stirring, in the solution previously obtained. Depending on polymer solubility, this either dissolves in the solution or forms a gel or a suspension having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogeneous suspension. The order of these steps can be reversed. The solvent employed can be aqueous or organic (for example ethanol). For example demineralized water can be used.

The active ingredient concentration in the suspension is from 1 to 40% by weight, preferably from 10 to 25%.

The hydrophilic polymer concentration in the suspension is from 5 to 40% by weight, preferably 10 to 25%.

The surfactant concentration in the suspension is from 0 to 10% by weight, preferably below 5%.

The invention also covers this novel suspension.

Without wishing to be tied down to a specific theory, applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-agglomerated form.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

Preparation of a pharmaceutical composition of fenofibrate according to the invention.

A composition containing, as the element a), micronized fenofibrate, Plasdone®, Capsulac® and sodium lauryl sulfate was prepared.

The micronized fenofibrate had a particle size of about 5 µm, as measured using a Coulter counter.

The Plasdone K25® corresponds to a polyvinylpyrrolidone PVP ISP and the Capsulac 60® corresponds to a coarse crystal lactose monohydrate (Meggie) (particle size between 100 and 400 µm).

The sodium laurylsulfate (7 g) is dissolved in water (demineralized water, 1750 g) and the micronized fenofibrate (350 g) is put into suspension in the mixture obtained (for example using a helix stirrer at 300 rpm for 10 minutes, then using an Ultra Turrax agitator at 10,000 rpm, for 10 minutes). Following this, the PVP (350 g) is added while still agitating, stirring (helix stirrer) being continued until the latter had dissolved (30 minutes). It is all passed through a sieve (350 µm) to eliminate possible agglomerates.

Separately, the lactose (400 g) is put into suspension in a fluidized air bed granulator (of the Glatt® GPCG1—Top Spray type or equivalent) and heated to a temperature of 40° C.

The fenofibrate suspension is sprayed onto the lactose. This step is carried out under the following conditions: spraying pressure: 2.1 bar, air throughput 70 m³/h, air inlet temperature: 45° C.; air outlet temperature: 33° C.; product temperature 34° C.; duration of spraying: 3 h.

The granulate thus obtained can be put inside capsules or transformed into tablets. Any suitable conventional technique for preparing such dosage forms can be used.

8

For transformation to tablet form, one will mix 191 g of the granulate obtained (using for example a mixer-grinder type mixing apparatus, a planetary mixer or turn-over mixer), with the outer phase having the following composition:

56 g Polyplasdone XL® (cross-linked polyvinylpyrrolidone ISP, as described in the USA Pharmacopoeia "USP-NF" under the name of crospovidone, mean molecular weight > 1,000,000);

88 g Avicel® PH200 (microcrystalline cellulose);

3.5 g sodium stearyl fumarate (Mendell, U.S.A.); and

2 g Aerosil® 200 (colloidal silica).

The cross-linked polyvinylpyrrolidone, the microcrystalline cellulose, the sodium stearyl fumarate and the colloidal silica are respectively, disintegration agents, binders, lubricating and flow enhancing agents.

The tablet can be obtained on an alternating compression machine (for example Korsch EKO) or a rotary machine (for example Fette Perfecta 2).

One thus obtains tablets having the following composition, expressed in mg:

element (a):

micronized fenofibrate	100.0
PVP	100.0
Lactose	114.3
sodium laurylsulfate	7.0

outer phase (or layer):

cross-linked PVP	92.7
microcrystalline cellulose	145.7
sodium stearyl fumarate	5.8
colloidal silica	3.3

EXAMPLE 2

Dissolution of a composition according to the invention and a composition according to the prior art.

a) Dissolution Medium and Procedure for Measuring Dissolution.

A dissolution medium which is discriminating, in other words one in which two products having very different dissolution profiles in gastric juices will have very different dissolution curves is looked for.

For this, an aqueous medium containing a surfactant, this being Polysorbate 80 (polyoxyethylene sorbitane monooleate) is used. This surfactant is readily available from various suppliers, is the object of a monograph in the Pharmacopoeias, and is thus easy to implement (being also a water-soluble liquid product). Other surfactants can also be used.

The rotating blade method (European Pharmacopoeia) is used under the following conditions: volume of medium: 1200 ml; medium temperature: 37° C.; blade rotation speed: 75 rpm; samples taken: every 2.5 minutes. Determination of the amount dissolved is carried out by spectrophotometry. Test are repeated 6 times over.

b) Results

The composition according to the invention consisted of two tablets containing about 100 mg fenofibrate prepared according to Example 1.

US 6,652,881 B2

9

The prior art composition was Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate (corresponding to capsules of 200 mg fenofibrate, co-micronized with sodium laurylsulfate, and containing lactose, pre-gelatinized starch, cross-linked polyvinylpyrrolidone and magnesium stearate, in line with the teachings of EP-A-0330532).

The results obtained are shown graphically in FIG. 1, in which the percentage of dissolution is shown, the observed standard deviation being indicated between brackets.

These results clearly show that the compositions according to the invention have a dissolution profile which is distinctly better than that of the prior art compositions.

These results also clearly show that with the compositions of the invention, the standard deviation observed is distinctly lower than is the case with prior art compositions.

EXAMPLE 3

Study of bioavailability of compositions according to the invention and prior art compositions.

A test of bioavailability on healthy volunteers was carried out.

The following compositions were tested:

composition according to the invention: capsules containing granules prepared according to example 1, containing 200 mg fenofibrate.

first composition according to the prior art: Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate, identical to that in the previous example.

second prior art composition: Secalip® in capsule form (300 mg fenofibrate in the form of three 100 mg capsules).

The study was carried out on 6 healthy volunteers receiving a single dose of fenofibrate, with a minimum 6-day rest period between administrations. The samples for pharmacokinetic analysis were collected after each administration at the following times: 0.5 h; 1 h; 2 h; 3 h; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h; 24 h; 36 h; 48 h; 72 h; and 96 hours following administration of the medicament. Fenofibric acid content in plasma was measured for each sample.

The results obtained are given in table 1 below.

TABLE 1

Product	dose (mg)	C _{max} (µg/ml)	t _{max} (h)	t _{1/2} (h)	AUC 0-4 (µg·h/ml)	AUC 0-∞ (µg·h/ml)
Invention	200	5.4	8	23	148	162
Secalip® 100	3 × 100	1.1	25	39	53	56
Lipanthyl® 200M	200	1.6	8.3	41	71	92

C_{max}: maximum plasma concentration
 t_{max}: time to reach C_{max}
 t_{1/2}: plasma half-life
 AUC 0-4: area under the curve from 0 to 4
 AUC 0-∞: area under the curve from 0 to ∞.

The results clearly show that the compositions of the present invention have a dissolution profile that is an improvement over compositions of the prior art, leading to a considerably enhanced bioavailability of the active ingredient compared to that obtained with compositions of the prior art.

10

EXAMPLE 4

Comparison of the dissolution profile of compositions according to the invention and that of products currently on the German market.

On the German market, immediate or sustained-release fenofibrate formulations exist. Like in France, the 100 mg and 300 mg (conventional) forms coexist with 67 and 200 mg forms (having enhanced bioavailability, according to the teaching of EP-A-0330532). These products are as follows:

Fenofibrate—Ratiopharm; Ratiopharm—Ulm;

Capsules;

Composition: 100 mg fenofibrate;

Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Durafenat; Durachemic—Wolfratshausen Capsules;

Composition: 100 mg fenofibrate;

Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Normalip pro; Knoll—Ludwigshafen;

Capsules;

Composition: 200 mg Fenofibrate;

Excipients: Croscopolidone, gelatine, monohydrate lactose, magnesium stearate, corn starch, sodium laurylsulfate, E 132 and E 171 colorants.

A comparison was made between:

the tablet of the invention as prepared using example 1 (2×100 mg)

Normalip pro® (200 mg);

Lipanthyl® 200M (200 mg) (according to the preceding example);

Fenofibrate by Ratiopharm® (2×100 mg);

Durafenat® (2×100 mg)

The tests were implemented under the same conditions as in the previous examples. FIG. 2 summarizes the results.

These results clearly show that the compositions of the invention have a distinctly improved dissolution compared to prior art compositions.

Obviously, the present invention is not limited to the embodiments described but may be subject to numerous variations readily accessible to those skilled in the art.

What is claimed is:

1. A composition comprising micronized fenofibrate, wherein the composition has a dissolution of at least 10% in

5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate.

2. The composition of claim 1, wherein the micronized fenofibrate has a size less than or equal to 20 microns.

US 6,652,881 B2

11

3. The composition of claim 1, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
4. The composition of claim 1, further comprising at least one polymer.
5. The composition of claim 1, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
6. An orally administrable tablet comprising micronized fenofibrate, wherein the tablet has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.
7. The tablet of claim 6, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
8. The tablet of claim 6, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
9. The tablet of claim 6, further comprising at least one polymer.
10. The tablet of claim 6, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
11. A composition comprising micronized fenofibrate and at least one polymer, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate.
12. The composition of claim 11, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
13. The composition of claim 11, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
14. The composition of claim 11, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
15. A composition comprising at least one inert carrier and one or more outer layers comprising micronized fenofibrate, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate.
16. The composition of claim 15, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
17. The composition of claim 15, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
18. The composition of claim 15, further comprising at least one polymer.
19. The composition of claim 15, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
20. The composition of claim 15 in the form of a tablet.
21. The composition of claim 15 in the form of a granulate.
22. A composition comprising granulates which comprise micronized fenofibrate; wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium consti-

12

- tuted by water with 2% by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.
23. The composition of claim 22, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
24. The composition of claim 22, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
25. The composition of claim 22, wherein the granulates further comprise at least one polymer.
26. The composition of claim 22, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
27. An orally administrable tablet comprising granulates, wherein the granulates comprise micronized fenofibrate, and wherein the tablet has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.
28. The tablet of claim 27, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
29. The tablet of claim 27, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
30. The tablet of claim 27, wherein the granulates further comprise at least one polymer.
31. The tablet of claim 27, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
32. An orally administrable capsule comprising granulates, wherein the granulates comprise micronized fenofibrate, and wherein the capsule has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using a rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium comprising water with 2% by weight polysorbate 80 or a dissolution medium comprising water with 0.025 M sodium lauryl sulfate.
33. The capsule of claim 32, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
34. The capsule of claim 32, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
35. The capsule of claim 32, wherein the granulates further comprise at least one polymer.
36. The capsule of claim 32, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.
37. A granulate comprising micronized fenofibrate, wherein the granulate has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.
38. The granulate of claim 37, wherein the micronized fenofibrate has a size less than or equal to 20 microns.
39. The granulate of claim 37, wherein the micronized fenofibrate has a size less than or equal to 10 microns.
40. The granulate of claim 37, further comprising at least one polymer.
41. The granulate of claim 37, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.

* * * * *

May 21, 2004

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21,612

NAME OF APPLICANT / NDA HOLDER

Cipher Pharmaceuticals Ltd

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Luxacor

ACTIVE INGREDIENT(S)

Fenofibrate

STRENGTH(S)

50, 100, 150. mg

b(4)

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,545,628

b. Issue Date of Patent

8/13/1996

c. Expiration Date of Patent

1/10/2015

d. Name of Patent Owner

Galephar PR

Address (of Patent Owner)

Road 198 km 14.7 Num 100

City/State

Juncos

ZIP Code

00777

FAX Number (if available)

(787) 713 0344

Telephone Number

(787) 713 0340

E-Mail Address (if available)

adeboeck@galephar.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

same as 1d above

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
Not applicable

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 11 - 15 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.
Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
For Type IIa, IIb, IV and V dyslipidemia

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
May 21, 2004



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Cipher Pharmaceuticals Ltd

Address

Suite 201
Lauriston

City/State

Collymore Rock
St. Michael, BARBADOS

ZIP Code

Telephone Number

N. American Contact 905 602 5840

FAX Number (if available)

N. American Contact 905 602 0628

E-Mail Address (if available)

landrews@cipherpharma.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

6/2/04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: June 2, 2004
FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
TO: NDA 21-612
Luxacor-(fenofibrate) capsules
Cipher Pharmaceuticals
SUBJECT: NDA review issues and recommended action

Background

This is a 505b2 application for a new fenofibrate product referencing Tricor (fenofibrate), manufactured by Abbott. The original application was received February 26, 2003 and an approvable action was taken on December 18, 2003 citing CMC deficiencies, and a new dissolution method was recommended. The sponsor submitted a complete response on March 30, 2004.

Safety

Efficacy

Labeling

Biopharmaceutics

There is a food effect with Luxacor, as there is with Tricor. Luxacor and Tricor were bioequivalent under high fat meal conditions. Under fasting conditions, extent of absorption (AUC) for Luxacor and Tricor were equivalent. Cmax was lower for Luxacor than for Tricor under fasting conditions. Both drugs are to be taken with food. No concerns about toxicity relative to Tricor are raised if patients were to take Luxacor without food.

Pharmacology/Toxicology

By reference.

Chemistry/ Microbiology

ONDC recommends approval. All deficiencies have been addressed.

Patent certification

Regulatory issues remain in this regard and are cited in the action letter. Once these are resolved, tentative approval can be granted.

Recommendation

Approvable, pending resolution of patent certification issues and labeling.

NDA # 21-612

Drug: Luxacor (fenofibrate capsules)

Proposal: treatment of dyslipidemia referencing Tricor

06/02/04

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
6/2/04 05:22:58 PM
MEDICAL OFFICER

Appears This Way
On Original

NDA REGULATORY FILING REVIEW #2
(Including Memo of Filing Meeting)
AMENDED 505(B)(2) QUESTIONS

NDA # 21-612

Trade Name: Luxacor
Generic Name: fenofibrate capsules
Strengths: 50 mg, 100 mg, 150 mg, ~~200 mg~~

b(4)

Applicant: Cipher Pharmaceuticals, Inc.

Date of Application: March 30, 2004

Date of Receipt: April 2, 2004

Date clock started after UN: N/A

Date of Filing Meeting:

Filing Date:

Action Goal Date (optional): N/A

User Fee Goal Date: June 2, 2004

Indication(s) requested: Reduction of LDL-C, Total-C, TG, Apo-B, and increase HDL-C in adults with primary hypercholesterolemia (IIA & IIB) and adults with hypertriglyceridemia (Type IV & V).

Type of Original NDA: (b)(1) _____ (b)(2) X

OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete Appendix B. **Completion of Appendix B is mandatory for all 505(b)(2) applications, even if the other parts of this Regulatory Filing Review are not completed.**

Therapeutic Classification: S X

P _____

Resubmission after withdrawal? No

Resubmission after refuse to file? No

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted:

YES

User Fee Status:

Paid X Exempt (orphan, government) _____

Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for use that has not been approved under section 505(b).

Examples of a new indication for use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? N/A
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
If no, explain:
- If an electronic NDA, does it follow the Guidance? NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Partially electronic.
Additional comments:
- If in Common Technical Document format, does it follow the guidance? YES
- Is it an electronic CTD? NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:
- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers:
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 8/22/03
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

Appears This Way
On Original

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 15, 2003

BACKGROUND:

This is a 505(b)(2) NDA for fenofibrate capsules in ~~50 mg, 100 mg, 150 mg~~ strengths, 50 mg, 100 mg, 150 mg. The innovator, Abbott Laboratories, is not marketing its approved 67 mg, 134 mg, or 200 mg capsules (NDA 19-304). However, Abbott is marketing tablets approved in 54 mg and 160 mg strengths (NDA 21-203).

b(4)

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Mary Parks, M.D.
Secondary Medical:	N/A
Statistical:	J. Todd Sahlroot, Ph.D.
Pharmacology:	Indra Antonipillai, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Mike Adams, Ph.D.
Environmental Assessment (if needed):	Mike Adams, Ph.D.
Biopharmaceutical:	Wei Qiu, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
Regulatory Project Management:	Valerie Jimenez
Other Consults:	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY NA X FILE _____ REFUSE TO FILE _____

STATISTICS FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS	FILE <u> X </u>	REFUSE TO FILE _____
• Biopharm. inspection needed:		YES
PHARMACOLOGY	NA _____ FILE <u> X </u>	REFUSE TO FILE _____
• GLP inspection needed:		NO
CHEMISTRY	FILE <u> X </u>	REFUSE TO FILE _____
• Establishment(s) ready for inspection?		YES
• Microbiology		N/A

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- X No filing issues have been identified.
- _____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Valerie Jimenez
Regulatory Project Manager, HFD-

Appears This Way
On Original

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to published general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appears This Way
On Original

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 21-203 Tricor Tablets, 54 mg and 160 mg/Abbott Laboratories

3. The purpose of the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should thus be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the proposed 505(b)(2) application that is already approved?

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) (ORP)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) (ORP) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative" as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a change in dosage strength and dosage form. The reference listed drug is 54 mg and 160 mg Tablets whereas the application contains 50 mg, 100 mg, 150 mg, ~~160 mg~~ Capsules.

b(4)

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). NO

10. Are there certifications for each of the patents listed for the listed drug(s)?

NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA (Paragraph I certification).

Patent No. 6,180,138 Abott 1/30/01

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired (Paragraph II certification).

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire (Paragraph III certification).

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted (Paragraph IV certification).

Patent Numbers: 4,895,226

6,652,881 B2 expires January 9, 2018, Paragraph IV, no proof of notification
6,074,670 and 6,277,405 B1, Fournier received notice 3/17/03 and Abbott received
notice 3/14/03.
6,589,552 no Cipher certification or proof of notification submitted

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications (Section viii statement).

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent No. 5,545,628 Galaphar PR, Inc. (owner)

On April 21, 2003, Abbott Laboratories and Fournier filed a patent infringement suit for Patent No. 6,277,405.

NO Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? YES
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).? N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). N/A
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. N/A
- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
6/2/04 01:01:27 PM
CSO

Appears This Way
On Original

6/2/04

Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-612

Name of Drug: Luxacor (fenofibrate capsules), 50 mg, 100 mg, 150 mg. _____

b(4)

Sponsor: Cipher Pharmaceuticals, Inc.

Materials Reviewed:

Submission Date(s): Draft Labeling: Package Insert (PI), carton and container labels, March 30, 2004

Background and Summary

The revised draft labeling was submitted on March 30, 2004, in response to an approvable letter issued on December 18, 2003. Luxacor, a 505(b) (2) application, is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Type IIa, IIb, IV, and V). The reference listed drug is Tricor Tablets, 54 mg and 160 mg strengths for Luxacor Capsules, 50 mg, 100 mg, 150 mg, _____ strengths.

b(4)

Review

Package Insert

The submitted label (March 30, 2004) was compared to the annotated label (December 24, 2002), which delineated the differences from the current Tricor Tablet labeling. The following revisions have been made:

1. The trade name "*CIP-FENOFIBRATE*" was changed to "*LUXACOR*" throughout the labeling.
2. Under the DESCRIPTION section, "_____ was replaced with "Gelucire 44/14 (lauryol macrogol glycerides type 1500).
3. Under the DESCRIPTION section, "_____ was replaced with "polyethylene glycol 20, 000" and "polyethylene glycol 8000".
4. Under the DESCRIPTION section, "gelatin and titanium dioxide" were added.
5. Under the CLINICAL PHARMACOLOGY section, Pharmacokinetics/Metabolism subsection, "*CIP-FENOFIBRATE*" was changed to "*LUXACOR*".
6. Under Pharmacokinetics/Metabolism, the Absorption section was changed from:

b(4)

b(4)

"The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers,

approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces.

The absorption of fenofibrate is increased when administered with food. _____

b(4)

To

b(4)

The extent of absorption of LUXACOR in terms of AUC value of fenofibric acid increased in a less than proportional manner while the rate of absorption in terms of C_{max} value of fenofibric acid increased proportionally related to dose.”

7. Under Pharmacokinetics/Metabolism, the Distribution section was changed from:

b(4)

To

“In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved after 5 days of once a day dosing and demonstrated a mean 2.4-fold accumulation following multiple dose administration. Steady-state plasma levels of fenofibrate demonstrated not accumulation. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.”

8. Under the PRECAUTIONS section, *Carcinogenesis and Mutagenesis* was changed from:

b(4)

b(4)

To

Carcinogenesis and Mutagenesis

“Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45 and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD, based on mg/m² of surface area). At a dose of 200 mg/kg/day (at 6 times MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/m² surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg; 2 times the human dose), and gemfibrozil (250 mg/kg; 2 times the human dose, multiples based on mg/m² surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular nodules in females. Gemfibrozil increased hepatic neoplastic nodules in females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45 and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at same doses, fenofibrate 10, 45 and 200 mg/kg/day (approximately 0.2, 0.7 and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD."

9. Under the **PRECAUTIONS** section, *Teratogenic Effects, Pregnancy Category C* was changed from:

b(4)

To

“Teratogenic Effects, Pregnancy Category: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/m^2 surface area). There are no adequate and well controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration approximately 9 times the MRHD of fenofibrate to female rats before and throughout gestation caused _____ of dams to delay delivery and resulted in 60% increase in

post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight at birth, as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams, and death in 7% of fetuses at 18 times the MRHD."

10. Under the **DOSAGE AND ADMINISTRATION** section, the first sentence "~~.....~~

~~.....~~ was deleted.

b(4)

11. The **HOW SUPPLIED** section was revised from:

To

b(4)

b(4)

12. Under the Storage section, the statement ' ~~_____~~ ' was changed to "Protect from moisture and light."

b(4)

The above modifications are acceptable per the response to the December 18, 2003, Approvable letter. They are acceptable and comply with the FDA requests; however, the biopharmaceutics reviewer has requested further revisions to the Pharmacokinetics/Metabolism section, Absorption subsection in her May 13, 2004, review.

The following underlined text in the Pharmacokinetics/Metabolism section, Absorption and Metabolism subsections, were included in the December 22, 2002, submission, however were inadvertently left out of the March 30, 2004, submission and should be included in the labeling.

To the Pharmacokinetics/Metabolism section, Absorption subsection, the underlined text should be added as the first and second paragraphs under this heading.

Absorption

"The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces.

The absorption of fenofibrate is increased when administered with food."

To the Pharmacokinetics/Metabolism section, Metabolism subsection, the underlined text should be added as the last two paragraphs.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; unchanged fenofibrate is detected at low concentrations in plasma compared to fenofibric acid over most of the single dose and multiple dosing periods.

"Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent."

Additional labeling changes that are required per the Biopharmaceutics review dated May 13, 2004, are as follows:

Note: Under the Pharmacokinetics/Metabolism section, Absorption subsection, the biopharmaceutics review requested that the text " ~~_____~~ " be removed from the below paragraph; "

b(4)

The paragraph should read as follows:

Container Labels

The draft bottle labels submitted on December 24, 2002, were compared to the submitted draft labels (March 30, 2004). The following changes were made to the 50 mg, 100 mg, 150 mg, trade (30 and 90 count bottles) and Physician sample size (7-count):

13. NDC numbers were added to all container labels.
14. The trade name "_____ " was added to all container labels.
15. _____ was added to all container labels.
16. The statement "_____
_____ was changed to "Usual Adult
Dosage: See accompanying package insert."
17. _____ was changed to '_____
18. _____ was changed
to "_____
19. The following text was added:

The changes to the container labels are satisfactory per the Chemistry Review dated May 21, 2004, except the firm should be reminded to comply with the requirement at 21 CFR 201.10(g)(2) that the established name must be at least one half the height of the proprietary name.

Conclusion

The biopharmaceutics review dated May 13, 2004, requests additional changes to the CLINICAL PHARMACOLOGY section. Another AE letter should request the additional labeling changes and include the 21 CFR 201.10 (g)(2) reminder and request proof of Paragraph 4 notification for two patents remaining. The NDA cannot be approved now because a patent infringement suit is pending.

Valerie Jimenez
Regulatory Project Manager, HFD-510

Appears This Way
On Original

b(4)

b(4)

b(4)

b(4)

b(4)

b(4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
6/2/04 03:07:01 PM
CSO

Appears This Way
On Original

RECEIVED

JUN 02 2004

CDR / CDER

June 1, 2004

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

RECEIVED

JUN 03 2004

FDR/CDER

N 0000

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg
Request for additional information: 150 mg

b(4)

Dear Dr. Orloff:

We refer to a discussion between Dr. Mary Parks, Ms. Valerie Jimenez and _____
(Cipher Pharmaceuticals Ltd) on May 25, 2004. Dr. Parks had requested that Cipher
Pharmaceuticals Ltd. should consider _____

b(4)

_____ Dr. Parks also noted that there was no
evidence presented to support bioequivalence between Cipher's 150 mg product and the 160
mg strength of the reference listed drug, Tricor.

b(4)

_____ Study FENPK.01.03
(PMRI 01-399) established that the product (all strengths of which are homotetic i.e. they all
have the same composition and strengths vary only by fill weight) exhibits linear
pharmacokinetics with respect to dose within the 50 to 200 mg dose range that was measured
(Reference NDA Module 2, Section 2.7.1.2). This is noted in the current draft of the package
insert, under Pharmacokinetics/Metabolism:

b(4)

_____ With respect to potential concerns regarding having available _____ strengths which are so close,
Cipher Pharmaceuticals Ltd. notes that the Dosing and Administration section of the current
draft of the package insert states:

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Limited	DATE OF SUBMISSION June 1, 2004
TELEPHONE NO. (Include Area Code) NA Contact (905) 602-5840	FACSIMILE (FAX) Number (Include Area Code) (905) 602-0628
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, BARBADOS	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873 Puerto Rico Tel: (787) 713-0340 Fax: (787) 713-0344

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY LUXACOR	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: For Type IIa, IIb, IV and V dyslipidemia		RECEIVED JUN 02 2004

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	CDR / CDER
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input checked="" type="checkbox"/> 505 (b)(2)	
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug	Tricor Tablets	Holder of Approved Application	Abbott Laboratories
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY	<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30	<input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION	Response to FDA request for additional information: 150 mg		
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED	1	THIS APPLICATION IS	<input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
Please refer to original NDA #21,612 for Establishment Information.			

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA#21,612

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (i)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to FDA request for additional information: 150 mg and 160 mg

CERTIFICATION

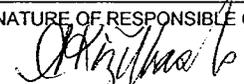
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Larry Andrews, President, Cipher Pharmaceuticals Ltd. Arthur M. Deboeck, Vice President & General Manager	DATE: June 1, 2004
ADDRESS (Street, City, State, and ZIP Code) U.S. Agent, Galephar P.R. Inc. See attachment for address & contact numbers	Telephone Number Cipher: (905) 602-5840 Galephar: (787) 713-0340	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. Applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is

Paper Paper and Electronic Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

Jimenez, Valerie

From: Jimenez, Valerie
Sent: Friday, May 28, 2004 3:24 PM
To: Parks, Mary H
Subject: NDA 21-612/Luxacor Trade Name

Mary,
Per your email of May 14, 2004, and the trade name consultation response of
April 28, 2004. ~~_____~~ was notified that the trade
name ~~_____~~ was not found acceptable by the Agency.
Thank you,
Valerie

b(4)

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
5/28/04 03:23:48 PM
CSO

Appears This Way
On Original

5/20/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-612

Galaphar PR Inc., Agent for
Cipher Pharmaceuticals Ltd.
Attention: Arthur M. Deboeck
Vice President and General Manager
Road 198 No. 100 km 14.7, Juncos Industrial Park
Juncos, PR 00777-3873

Dear Mr. Deboeck:

We acknowledge receipt on April 2, 2004, of your March 30, 2004, resubmission to your new drug application for Luxacor (fenofibrate) Capsules, 50 mg, 100 mg, 150 mg, ~~150 mg~~

b(4)

We consider this a complete, class 1 response to our December 18, 2003, action letter. Therefore, the user fee goal date is June 2, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies in all pediatric groups for this application.

If you have any question, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks
5/21/04 10:37:14 AM
for Dr. Orloff

Appears This Way
On Original

ORIGINAL

May 21, 2004

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

RECEIVED

MAY 24 2004

CDR / CDER

RECEIVED

MAY 25 2004

FDR/CDER

N000(XP)

NEW CORRESP

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg,
Request for additional information: Forms 3542a and 3454

b(4)

Dear Dr. Orloff:

We refer to a request for additional information from Ms. Valerie Jimenez on May 20, 2004. In response to that request please find enclosed the following:

- Completed FDA Form 3542a
- Completed FDA Form 3454

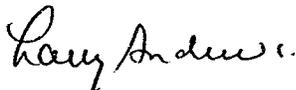
It is our understanding from subsequent communication with Ms. Jimenez that the debarment certification provided as part of the March 30, 2004 response may indeed meet the Agency's requirements. If not, please advise and we will send a revised version.

If you have any questions or comments, please do not hesitate to call me at 905 602 5840 x 24, or you can contact _____

b(4)

_____ regarding this submission, or on other related matters.

Yours sincerely,



Larry Andrews
President
Cipher Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Limited	DATE OF SUBMISSION May 21, 2004
TELEPHONE NO. (Include Area Code) NA Contact (905) 602-5840	FACSIMILE (FAX) Number (Include Area Code) (905) 602-0628
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, BARBADOS	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873 Puerto Rico Tel: (787) 713-0340 Fax: (787) 713-0344

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY LUXACOR	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: For Type IIa, IIb, IV and V dyslipidemia		

RECEIVED
MAY 24 2004

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug	Tricor Tablets	Holder of Approved Application
		Abbott Laboratories
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	
	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	
	<input type="checkbox"/> RESUBMISSION	
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> OTHER	
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY	<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30
	<input type="checkbox"/> Prior Approval (PA)	
REASON FOR SUBMISSION		
Response to FDA request for additional information		
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED	1	THIS APPLICATION IS
		<input checked="" type="checkbox"/> PAPER
		<input type="checkbox"/> PAPER AND ELECTRONIC
		<input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Please refer to original NDA #21,612 for Establishment Information.		

CDR / CDER

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA#21,612

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Response to FDA request for additional information re particle size distribution

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Larry Andrews, President, Cipher Pharmaceuticals Ltd. Arthur M. Deboeck, Vice President & General Manager	DATE: May 21, 2004
---	--	-----------------------

ADDRESS (Street, City, State, and ZIP Code) U.S. Agent, Galephar P.R. Inc. See attachment for address & contact numbers	Telephone Number Cipher: (905) 602-5840 Galephar: (787) 713-0340
---	--

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852
--	--

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

cipher
Pharmaceuticals Limited

ORIGINAL

N1000 BC
ORIG AMENDMENT

May 14, 2004

RECEIVED

MAY 17 2004

CDR / CDER

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

RECEIVED

MAY 18 2004

FDR/CDER

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg,
FDA Request for Additional Information re particle size distribution

b(4)

Dear Dr. Orloff:

We refer to telephone communications between Valerie Jimenez _____ on May 10 and 11, 2004. The Agency had requested additional information from Ciper regarding particle size distribution of the Ciper's product as released in the gastrointestinal tract.

b(4)

Ciper's fenofibrate capsules are prepared by _____

b(4)

_____. In other words, _____,

_____. As a result, Ciper is unable to provide information regarding particle size distribution of fenofibrate as released in the gastrointestinal tract.

It is our understanding that this request does not affect the progress of the ongoing review of NDA 21-612.

If you have any questions or comments, please do not hesitate to call me at 905 696 9380 x 24, or you can contact _____

b(4)

_____ regarding this submission, or on other related matters.

Yours sincerely,

Larry Andrews

Larry Andrews
President
Ciper Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663 Fax: (246) 228-8329

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Limited	DATE OF SUBMISSION May 14, 2004
TELEPHONE NO. (Include Area Code) NA Contact (905) 602-5840	FACSIMILE (FAX) Number (Include Area Code) (905) 602-0628
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, BARBADOS	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873 Puerto Rico Tel: (787) 713-0340 Fax: (787) 713-0344

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY LUXACOR	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: For Type IIa, IIb, IV and V dyslipidemia		

RECEIVED

MAY 17 2004

b(4)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug	Tricor Tablets	Holder of Approved Application
		Abbott Laboratories
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY		
	<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30
	<input type="checkbox"/> Prior Approval (PA)	
REASON FOR SUBMISSION Response to FDA request for additional information re particle size distribution		
PROPOSED MARKETING STATUS (check one)		
	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED	1	THIS APPLICATION IS
		<input checked="" type="checkbox"/> PAPER
		<input type="checkbox"/> PAPER AND ELECTRONIC
		<input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Please refer to original NDA #21,612 for Establishment Information.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		
NDA#21,612		

CDR / CDER

This application contains the following items: <i>(Check all that apply)</i>	
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling <i>(check one)</i> <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER <i>(Specify)</i> Response to FDA request for additional information re particle size distribution

CERTIFICATION

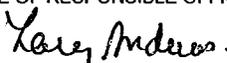
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Larry Andrews, President, Cipher Pharmaceuticals Ltd. Arthur M. Deboeck, Vice President & General Manager	DATE: May 14, 2004
ADDRESS <i>(Street, City, State, and ZIP Code)</i> U.S. Agent, Galephar P.R. Inc. See attachment for address & contact numbers	Telephone Number Cipher: (905) 602-5840 Galephar: (787) 713-0340	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
101 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. Applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is

Paper Paper and Electronic Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

cipher

Canada Inc.

409 Matheson Blvd E
Mississauga, Ontario
L4Z 2H2
Tel. (905) 602-5840
Fax (905) 602-0628

Fax

To:	Valerie Jimenez	From:	Arshi Kizilbash, MD
Fax:	(301) 443-9282	Pages:	7 (including cover page)
Company	: FDA Div of Metabolic and Endocrine Drug Products	Date:	May 5, 2004
Re:	NDA: 21,612	CC:	

If you do not receive a complete transmission, please call: (905) 602-5840

● **Comments:**

FYI.

This fax transmission is privileged and contains confidential information intended only for the person(s) named above. Any other distribution, copying or disclosure is strictly prohibited. If you have received this fax transmission in error, please notify the sender immediately and destroy these pages promptly. We thank you for your cooperation.

cipher

Pharmaceuticals Limited

May 5, 2004

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg.
Revised Request for Waiver of Pediatric Studies

b(4)

Dear Dr. Orloff:

We refer to our new drug application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. We also refer to our submissions dated January 10, March 24, May 6, October 15, November 7, December 2 and 8, 2003, and the Complete Response to the FDA letter of December 18, 2003, which was submitted on March 30, 2004.

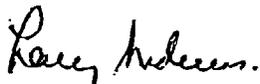
On May 3, 2004, Ms. Valerie Jimenez noted that the Request for Waiver of Pediatric Studies which was included in the original NDA was inconsistent with the revised form 356h which was submitted on December 8, 2003, with respect to the indications listed. As requested, please find enclosed a revised Request for Waiver of Pediatric Studies which lists the same indications as those included in the revised form 356h which was submitted on December 8, 2003 i.e. Types IIa, IIb, IV and V dyslipidemia.

If you have any questions or comments, please do not hesitate to call me at 905 696 9380 x 24, or you can contact ~~_____~~

b(4)

this submission, or on other related matters.

Yours sincerely,



Larry Andrews
President
Cipher Pharmaceuticals Ltd.

CC: Arthur DeBoeck, Galephar PR Inc.

b(4)

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663 Fax: (246) 228-8329

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0338 Expiration Date: August 31, 2005 See OMB Statement on page 2.	
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		FOR FDA USE ONLY	
		APPLICATION NUMBER	
APPLICANT INFORMATION			
NAME OF APPLICANT Cipher Pharmaceuticals Limited		DATE OF SUBMISSION May 5, 2004	
TELEPHONE NO. (Include Area Code) NA Contact (905) 602-5840		FACSIMILE (FAX) Number (Include Area Code) (905) 602-0628	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, BARBADOS		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park Juncos 00777-3873 Puerto Rico Tel: (787) 713-0340 Fax: (787) 713-0344	
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-612			
ESTABLISHED NAME (o.g., Proper name, USP/USAN name) Fenofibrate		PROPRIETARY NAME (trade name) IF ANY LUXACOR	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)		CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral	
(PROPOSED) INDICATION(S) FOR USE: For Type (Ia, Ib, IV and V dyslipidemia)			
APPLICATION INFORMATION			
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Tricor Tablets</u> Holder of Approved Application <u>Abbott Laboratories</u>			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION Correction of information related to proposed indications as submitted in original NDA dated December 24, 2002			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC			
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please refer to original NDA #21,612 for Establishment information.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) NDA#21,612			

b(4)

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Revised Request for Waiver of Pediatric Studies

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Larry Andrews</i>	TYPED NAME AND TITLE Larry Andrews, President, Cipher Pharmaceuticals Ltd. Arthur M. Deboeck, Vice President & General Manager	DATE: May 5, 2004
ADDRESS (Street, City, State, and ZIP Code) U.S. Agent, Galephar P.R. Inc. See attachment for address & contact numbers		Telephone Number Cipher: (905) 602-5840 Galephar: (787) 713-0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. Applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is

Paper Paper and Electronic Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Sponsor: Cipher Pharmaceuticals Limited
Product: CIP-Fenofibrate (fenofibrate capsules) – 50, 100, 150, ~~200~~ mg strengths
Indications(s): Type IV and V hypercholesterolemia

b(4)

1. What age ranges are included in your waiver request?

All pediatric age groups.

2. Reasons for waiving pediatric studies:

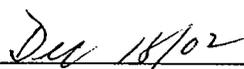
- (a) No meaningful therapeutic benefit over existing treatments **and** is unlikely to be used in a substantial number of pediatric patients
- (b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed
- (c) The product would be ineffective or unsafe in all pediatric age groups
- (d) Attempts to develop a pediatric formulation for a specific age group have failed
- (e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)
- Alzheimer's disease Age-related macular degeneration
 - Prostate Cancer Breast cancer
 - Renal cell cancer Non-germ cell ovarian cancer
 - Hairy cell cancer Pancreatic cancer, colorectal cancer
 - Osteoarthritis Squamous cell cancers of the oropharynx
 - Uterine cancer Basal cell and squamous cell cancer
 - Endometrial cancer Small cell and non-small cell lung cancer
 - Parkinson's disease Amyotrophic lateral sclerosis
 - Arteriosclerosis Symptoms of menopause
 - Infertility Other (please state and justify)

3. Justification for waiver (not necessary if category 2(e) is checked):

Fenofibrate is typically not beneficial until patients reach maturity.



Dr. Ian W. French Ph.D.
Chairman and Chief Scientific Officer



Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-612

Galephar PR Inc., US Agent for
Cipher Pharmaceuticals, Inc.
Attention: Authur M. Deboeck
Vice President and General Manager
Road 198 No. 100 km 14.7, Juncos Industrial Park
Juncos, PR 00777-3873

Dear Mr. Deboeck:

Please refer to the meeting between representatives of your firm and FDA on February 23, 2004. The purpose of the meeting was to clarify comments in the December 18, 2003, action letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 23, 2004

TIME: 12:00 noon – 1:00 p.m.

LOCATION: DMEDP Conference Room, 14B-39.

SPONSOR: Cipher Pharmaceuticals, Ltd.

TYPE OF MEETING: Type C

DRUG: Luxacor (fenofibrate) Capsules

APPLICATION: NDA 21-612

MEETING CHAIR: Stephen K. Moore, Ph. D., Chemistry Team Leader,
Division of Metabolic and Endocrine Drug Products (DMEDP)

MEETING RECORDER: Valerie Jimenez, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Stephen K. Moore, Ph. D.	Chemistry Team Leader	DMEDP, HFD-510
2. Mike Adams, Ph. D.	Chemistry Reviewer	DMEDP, HFD-510
3. Wei Qiu, Ph. D.	Chemistry Reviewer	DMEDP, HFD-510
4. Valerie Jimenez	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. _____	Consultant	Cipher Pharmaceuticals
2. Arthur Deboeck	Vice President and General Manager	Galephar PR, Inc.
3. Ileana Diez	Scientific Director	Galephar PR, Inc.

b(4)

BACKGROUND:

On February 9, 2004, the sponsor requested a guidance meeting to discuss further clarification of comments regarding the December 18, 2003, action letter.

MEETING OBJECTIVE:

Obtain input from the Agency regarding the chemistry and biopharmaceutics issues in the December 18, 2003, action letter.

DISCUSSION:

Questions from the action letter:

Question 7(a) Regarding the **proposed analytical methods** “Revise the methods for Content Uniformity (SOP 633.83) and Dissolution (SOP 633.84) to use reference standards and sample solution concentrations which are approximately the same.

Based on Cipher’s calculations, the solution concentrations cited above are already approximately the same. Could the Agency please provide further clarification of which concentrations are at odds?

FDA’s response:

- *The Agency stated that the reviewer’s calculations showed a very large difference between the concentrations of the sample solution and the reference standard solutions. The submitted calculations showed that the difference was much less and was acceptable. The difference was attributed to either something missed by the reviewer or a statement missing in the method description. It was concluded that the submitted calculations would be considered an adequate response to the comment. The firm agreed to submit the information that was provided for this meeting.*

Point (C) at the end of the letter “Identity [sic] the tests to be performed for the acceptance of each lot of each ingredient and for the nitrogen gas”.

Cipher believes that the tests for the acceptance of each lot have already been identified by test reference number in the NDA, and has interpreted this comment to mean that the Agency would like to have copies of each of the tests to be performed. Could the Agency please confirm that this interpretation is correct?

FDA’s response:

- *The Agency stated that, qualification of the supplier, acceptance of excipient lots would be based on a supplier Certificate of Analysis (COA) and the performance of an identity test. The identity tests were not specified in the NDA. It was concluded that a list of identity tests would be a sufficient response to the comment. The firm agrees to submit a complete list of these tests.*

Additional Recommendations:

- *The Agency notified the firm that the dissolution method and specifications should be revised to:*
Apparatus Type: USP apparatus 2 (Paddles)
Rotation Speed: 75 rpm
Medium: 2% Tween 80 and 0.1% pancreatin at pH 6.8, 37°C
Specification: _____
- *This specification was based on the data obtained from _____ capsules for each strength. The data showed that each individual capsule dissolved more than _____ for all strengths. The sponsor should submit additional dissolution data for _____ units from _____ lots for each strength to justify any modification of the specification.*

b(4)

b(4)

b(4)

Minutes Prepared by /s/ 2/23/04

Valerie Jimenez
Project Manager, HFD-510

Chair Concurrence: /s/ 4/22/04

Stephen K. Moore, Ph. D.
Chemistry Team Leader, HFD-510

MEETING MINUTES

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
4/23/04 09:44:03 AM

Appears This Way
On Original

cipher
Pharmaceuticals Limited

ORIGINAL
RECEIVED

March 30, 2004

APR 02 2004

CDR / CDER

David G. Orloff, M.D.
Director

Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

RECEIVED

APR 06 2004

FDR/CDER

N 000 BZ
ORIG AMENDMENT

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg,
Complete Response to FDA letter of December 18, 2003

b(4)

Dear Dr. Orloff:

We refer to our new drug application (NDA) dated December 24, 2002 and received by FDA on February 26, 2003. We also refer to our submissions dated January 10, March 24, May 6, October 15, November 7, December 2 and 8, 2003. The submission dated November 7, 2003 has been incorporated by specific reference as part of our response to question 10 in your letter of December 18, 2003. We notified the Agency of our intent to respond to the December 18, 2003 letter in correspondence dated January 7, 2004.

Please find enclosed a complete response to your letter of December 18, 2003. This response consists of 4 volumes of original information, and two copies of the same. This submission includes revised draft labeling (clean and marked-up versions), one copy in paper format, and one copy in electronic format, as requested.

Please note that on February 16, 2004, we notified you of our intent to change the brand name for the fenofibrate product that is the subject of the pending application, NDA 21-612, from Luxacor to ~~_____~~. Since we have not yet been notified of the acceptability of the proposed new brand name ~~_____~~, all documentation that includes a brand name still refers to Luxacor. Once confirmation of the acceptability of ~~_____~~ has been received, all relevant documents will be revised to include the new brand name, and copies will be submitted to the NDA.

b(4)

b(4)

If you have any questions or comments, please do not hesitate to call me at 905 696 9380 x 24, or you can contact ~~_____~~

b(4)

this submission, or on other related matters.

Yours sincerely,

Larry Andrews

Larry Andrews
President

to use EDR label
[Signature]
4/14/04

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663 Fax: (246) 228-8329

CC: Arthur DeBoeck, Galephar PR Inc.

b(4)

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Ltd.	DATE OF SUBMISSION 3/30/04
TELEPHONE NO. (Include Area Code) 905 696 9380	FACSIMILE (FAX) Number (Include Area Code) 905 602 0628
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock St. Michael, Barbados	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar PR Inc. Road 198 No. 100 km 14.7 Juncos Industrial Park, Juncos 00777-3875

RECEIVED
APR 06 2004
FDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21,612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY Luxacor	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: For Type IIa, IIb, IV and V dyslipidemia		APR 02 2004

RECEIVED
APR 02 2004
CDR / CDER

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Complete response to FDA letter December 18, 2003
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 4 (in triplicate) THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please refer to original NDA # 21,612 for Establishment Information
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) DA # 21,612

b(4)

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Jan W. French, CSO Arthur M Deboeck, VP & General Manager	DATE: 3/30/04
ADDRESS (Street, City, State, and ZIP Code) US Agent, Galephar PR Inc., Juncos, Puerto Rico, 00777-3873		Telephone Number (787) 713 0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
DER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

7/23/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-612

Galephar PR Inc., US Agent for
Cipher Pharmaceuticals, Inc.
Attention: Authur M. Deboeck
Vice President and General Manager
Road 198 No. 100 km 14.7, Juncos Industrial Park
Juncos, PR 00777-3873

Dear Mr. Deboeck:

Please refer to the meeting between representatives of your firm and FDA on February 23, 2004. The purpose of the meeting was to clarify comments in the December 18, 2003, action letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Appears This Way
On Original

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 23, 2004

TIME: 12:00 noon – 1:00 p.m.

LOCATION: DMEDP Conference Room, 14B-39

SPONSOR: Cipher Pharmaceuticals, Ltd.

TYPE OF MEETING: Type C

DRUG: Luxacor (fenofibrate) Capsules

APPLICATION: NDA 21-612

MEETING CHAIR: Stephen K. Moore, Ph. D., Chemistry Team Leader,
Division of Metabolic and Endocrine Drug Products (DMEDP)

MEETING RECORDER: Valerie Jimenez, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Stephen K. Moore, Ph. D.	Chemistry Team Leader	DMEDP, HFD-510
2. Mike Adams, Ph. D.	Chemistry Reviewer	DMEDP, HFD-510
3. Wei Qiu, Ph. D.	Chemistry Reviewer	DMEDP, HFD-510
4. Valerie Jimenez	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. _____	Consultant	Cipher Pharmaceuticals
2. Arthur Deboeck	Vice President and General Manager	Galephar PR, Inc.
3. Ileana Diez	Scientific Director	Galephar PR, Inc.

b(4)

BACKGROUND:

On February 9, 2004, the sponsor requested a guidance meeting to discuss further clarification of comments regarding the December 18, 2003, action letter.

MEETING OBJECTIVE:

Obtain input from the Agency regarding the chemistry and biopharmaceutics issues in the December 18, 2003, action letter.

DISCUSSION:

Questions from the action letter:

Question 7(a) Regarding the proposed analytical methods "Revise the methods for Content Uniformity (SOP 633.83) and Dissolution (SOP 633.84) to use reference standards and sample solution concentrations which are approximately the same.

Based on Cipher's calculations, the solution concentrations cited above are already approximately the same. Could the Agency please provide further clarification of which concentrations are at odds?

FDA's response:

- *The Agency stated that the reviewer's calculations showed a very large difference between the concentrations of the sample solution and the reference standard solutions. The submitted calculations showed that the difference was much less and was acceptable. The difference was attributed to either something missed by the reviewer or a statement missing in the method description. It was concluded that the submitted calculations would be considered an adequate response to the comment. The firm agreed to submit the information that was provided for this meeting.*

Point (C) at the end of the letter "Identity [sic] the tests to be performed for the acceptance of each lot of each ingredient and for the nitrogen gas".

Cipher believes that the tests for the acceptance of each lot have already been identified by test reference number in the NDA, and has interpreted this comment to mean that the Agency would like to have copies of each of the tests to be performed. Could the Agency please confirm that this interpretation is correct?

FDA's response:

- *The Agency stated that, qualification of the supplier, acceptance of excipient lots would be based on a supplier Certificate of Analysis (COA) and the performance of an identity test. The identity tests were not specified in the NDA. It was concluded that a list of identity tests would be a sufficient response to the comment. The firm agrees to submit a complete list of these tests.*

Additional Recommendations:

- *The Agency notified the firm that the dissolution method and specifications should be revised to:*
Apparatus Type: USP apparatus 2 (Paddles)
Rotation Speed: 75 rpm
Medium: 2% Tween 80 and 0.1% pancreatin at pH 6.8, 37°C
Specification: _____
- *This specification was based on the data obtained from _____ capsules for each strength. The data showed that each individual capsule dissolved more than _____ for all strengths. The sponsor should submit additional dissolution data for _____ units from _____ lots for each strength to justify any modification of the specification.*

b(4)
b(4)
b(4)

Minutes Prepared by /s/ 2/23/04 _____
Valerie Jimenez
Project Manager, HFD-510

Chair Concurrence: /s/ 4/22/04 _____
Stephen K. Moore, Ph. D.
Chemistry Team Leader, HFD-510

MEETING MINUTES

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
4/23/04 09:44:03 AM

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM: Valerie Jimenez, HFD-510
(301) 827-9090

DATE February 23, 2004	IND NO.	NDA NO. 21-612	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT February 16, 2004
NAME OF DRUG Luxacor (fenofibrate) Tablets	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Lipid Altering (5)	DESIRED COMPLETION DATE July 9, 2004	

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This application was AE'd on December 18, 2003, and will be resubmitted. The firm has submitted general correspondence notifying the Agency of another trade name. Therefore, we are requesting your comments/review on the proprietary name of "_____ the first trade name review was finalized on November 6, 2003, for Luxacor. Please call if you need additional information, Valerie Jimenez, Regulatory Project Manager, (301) 827-9090.

b(4)

PDUFA DATE: Resubmission of application will be late March.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
2/24/04 11:45:20 AM

Appears This Way
On Original



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2004

To: Arthur M. Deboeck	From: Valerie Jimenez
Company: Cipher Pharmaceuticals, Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (787) 713-0344	Fax number: (301) 443-9282
Phone number: (787) 713-0340	Phone number: (301) 827-9090
Subject: Teleconference Granted	

Total no. of pages including cover: 1

Comments: The meeting regarding NDA 21-612 you have requested has been scheduled for the following:
Date: Monday, February 23, 2004
Time: 12 noon to 1:00 p.m.
Place: Teleconference

FDA Participants: Stephen K. Moore, Ph. D., Chemistry Team Leader
W. Mike Adams, Ph. D., Chemistry Reviewer
Wei Qiu, Ph. D., Biopharmaceutics Reviewer
Valerie Jimenez, Regulatory Project Manager

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Valerie Jimenez
2/23/04 03:08:55 PM
CSO

Appears This Way
On Original

RECEIVED
FEB 18 2004
FDR/CDER

February 16, 2004

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

N000(C)
NEW CORRESP

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg
Change in Brand Name

b(4)

Dear Dr. Orloff:

We refer to our previous letter of October 15, 2003 notifying you of the proposed name LUXACOR for the fenofibrate product that is the subject of the pending application, NDA 21-612. We now wish to notify you of our intention to use the brand name _____ We apologize for any inconvenience caused by this further change.

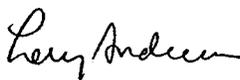
b(4)

If you have any questions or comments, please do not hesitate to call me at 905 696 9380 x 24, or you can contact _____

b(4)

_____ regarding this submission, or on other related matters.

Yours sincerely,



Larry Andrews
President
Cipher Pharmaceuticals Ltd.

Appears This Way
On Original

CC: FDA Central Document Room
Arthur DeBoeck, Galephar PR Inc.

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663 Fax: (246) 228-8329

A Drug Development Company

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Cipher Pharmaceuticals Ltd

DATE OF SUBMISSION

2/16/04

TELEPHONE NO. (Include Area Code)

905 696 9380

FACSIMILE (FAX) Number (Include Area Code)

905 602 0628

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Suite 201
Lauriston, Collymore Rock
St. Michael, Barbados

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Arthur M. Deboeck
Galephar PR Inc.
Road 198 No. 100 km 14.7
Juncos Industrial Park, Juncos 00777-3873

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21,612

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Fenofibrate

PROPRIETARY NAME (trade name) IF ANY

Luxacor

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM:

Capsules

STRENGTHS:

50, 100, 150 _____ mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

For Type IIa, IIb, IV and V dyslipidemia

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Change in Brand Name

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to original NDA # 21,612 for Establishment Information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA # 21,612

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Letter

CERTIFICATION

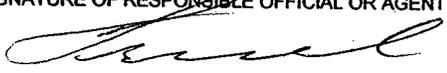
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Ian W. French, CSO Arthur M Deboeck, VP & General Manager	DATE: 2/16/04
ADDRESS (Street, City, State, and ZIP Code) US Agent, Galephar PR Inc., Juncos, Puerto Rico, 00777-3873		Telephone Number (787) 713 0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
101 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

cipher
Pharmaceuticals Limited

2/2/04 SUBMISSION
NO COVER LETTER

ORIGINAL

XP

RECEIVED

FEB 12 2004

FDR/CDER

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 6,652,881 B2

In accordance with the Federal Food, Drug and Cosmetic Act, as amended by Title XI of the Medicare Prescription Drug, Improvement and Modernization Act, Pub. L. No. 108-173, 117 Stat. 2066 (2003), and 21 C.F.R. § 314.50(i)(1)(i)(A)(4), a Patent Certification, and in particular a Paragraph IV Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv), as to U.S. Patent No. 6,652,881 B2 ("the '881 patent") is hereby provided for our New Drug Application ("NDA") No. 21-612 for Fenofibrate Capsules 50, 100, 150, — mg.

b(4)

Cipher Pharmaceuticals hereby certifies, pursuant to 21 U.S.C. § 355(b)(2)(A)(iv), that, in its opinion and to the best of its knowledge, the '881 patent, expiring on or about January 9, 2018, will not be infringed upon by the manufacture, use, sale, offer for sale or importation by Cipher Pharmaceuticals of Fenofibrate Capsules 50, 100, 150, — mg for which Cipher's application has been submitted, and/or that the '881 patent is invalid.

b(4)

STATEMENT CONCERNING NOTICE TO
PATENT OWNER AND NDA HOLDER

As required by Section 505(b)(3)(B) of the Federal Food, Drug and Cosmetic Act, as amended by Title XI of the Medicare Prescription Drug, Improvement and Modernization Act, Pub. L. No. 108-173, 117 Stat. 2066 (2003), Cipher hereby states that the notice required by Section 505(b)(3) and 21 C.F.R. § 314.52 has been concurrently sent to Abbott Laboratories Inc., as the holder of approved NDA No. 21-203 for Tricor[®] (fenofibrate) 54 mg and 160 mg tablets and the exclusive licensee of U.S. Patent No. 6,652,881 B2, and to _____ as the record owner of U.S. Patent No. 6,652,881 B2.

This notice to Abbott Laboratories Inc. and _____ has been sent by certified mail, return receipt requested, as required by 21 C.F.R. § 314.52(a).

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663; Fax: (246) 228-8329



Ian W. French
Chief Scientific Officer
Cipher Pharmaceuticals Ltd.

Feb 3, 2004
Date

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Ltd.	DATE OF SUBMISSION 2/3/04
TELEPHONE NO. (Include Area Code) Contact 905-696-938	FACSIMILE (FAX) Number (Include Area Code) 246-228-8329
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Suite 201 Lauriston, Collymore Rock ST. Michaels Barbados	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar P.R. Inc. Road 198 No. 100 km 14/7 Juncos Industrial Park Juncos, Puerto Rico 00777-3873 Tel: 787-713-0340 Fax: 787-713-0344

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-612		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fenofibrate	PROPRIETARY NAME (trade name) IF ANY CIP-Fenofibrate	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)		CODE NAME (If any)
DOSAGE FORM: Capsules	STRENGTHS: 50, 100, 150 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Tricor Tablets</u> Holder of Approved Application <u>Abbott Laboratories</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Paragraph IV Certification - a new US patent # 6,652,881 was listed in the Orange Book
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See original NDA for establishment information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ND 62,780; DMFs: _____

b(4)

b(4)

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

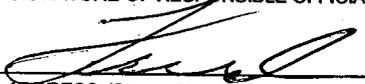
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Ian W. French, Ph.D., Chief Scientific Officer Arthur M. Deboeck, VP and General Manager	DATE: 2/3/04
ADDRESS (Street, City, State, and ZIP Code) , Arthur M. Deboeck, Galephar P. R. Inc. See original NDA for contact information		Telephone Number () Cipher: 905-696-9380 Galephar: 787-713-0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:



ORIGINAL

February 9, 2004

RECEIVED

FEB 12 2004

FDR/CDER

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fisher's Lane
Rockville, MD 20857

N 000 MR
ORIG AMENDMENT

Re: **NDA 21-612**
Luxacor (fenofibrate) Capsules 50 mg, 100 mg, 150 mg.

b(4)

Dear Dr. Orloff:

We refer to your letter of December 18, 2003 indicating that the above mentioned NDA is approvable once additional information has been provided, and our letter of January 7, 2004 indicating our intent to provide that additional information.

In order to finalize our response to your request, we require further clarification of a number of comments in the letter, specifically:

Question 7(a) Regarding the proposed analytical methods "Revise the methods for Content Uniformity (SOP 633.83) and Dissolution (SOP 633.84) to use reference standard and sample solution concentrations which are approximately the same.

Based on Cipher's calculations, the solution concentrations cited above are already approximately the same (see attached sheet). Could the Agency please provide further clarification of which concentrations are at odds?

Point (C) at the end of the letter "Identity [sic] the tests to be performed for the acceptance of each lot of each ingredient and for the nitrogen gas".

Cipher believes that the tests for the acceptance of each lot have already been identified by test reference number in the NDA, and has interpreted this comment to mean that the Agency would like to have copies of each of the tests to be performed. Could the Agency please confirm that this interpretation is correct?

Cipher has also requested clarification from Ms. Valerie Jimenez regarding FDA guidance on the inclusion of comparative bioavailability claims in product labeling, specifically the use of a comparator's brand name. It is proposed that this can be dealt with separately from the other requests for clarification in this letter.

Suite 201, Lauriston, Collymore Rock
St. Michael, Barbados
Tel: (246) 228-9663 Fax: (246) 228-8329

A Drug Development Company

In a telephone conversation with Ms. Jimenez on February 4, 2004, it was suggested that Cipher request a teleconference to clarify the above mentioned points relating to chemistry & manufacturing. Please consider this letter a request for a meeting by teleconference, unless it would be more efficient for the Agency to respond to the questions above in writing, which Cipher would certainly deem to be an acceptable approach.

Purpose of meeting:

Clarification of questions 7(a) and (C) in the December 18, 2004 approvable letter for NDA-21-612.

Proposed external attendees:

b(4)

Dr. Arthur DeBoeck, Galephar Inc, US Agent for Cipher Pharmaceuticals Ltd

Requested FDA participants:

Ms. Valerie Jimenez
CMC reviewer for NDA 21-612

Background information:

Provided above, and in attachment. No further information to be supplied.

Proposed dates:

February 10 - 13 inclusive
February 16 - 20 inclusive
February 23 - 24 inclusive

If you have any questions or comments, please do not hesitate to call me at 905 696 9380 x 24, or you can contact _____

b(4)

_____ regarding this submission, or on other related matters.

Yours sincerely,



Larry Andrews
President
Cipher Pharmaceuticals Ltd.

CC: FDA Central Document Room
Arthur DeBoeck, Galephar PR Inc.

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process