



March 5, 2003

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Re: Fenofibrate Capsules 50 mg, 100 mg, 150 mg, and 160 mg;
Notice of Paragraph IV Patent Certification Pursuant to
21 U.S.C. § 355(b)(3)(B) and 21 C.F.R. § 314.52.

Dear Sir or Madame:

This notice is provided pursuant to 21 U.S.C. § 355(b)(3)(B) and 21 C.F.R. § 314.52. Cipher Pharmaceuticals Ltd. ("Cipher") has submitted a New Drug Application pursuant to 21 U.S.C. § 355(b)(2) (a "505(b)(2) NDA"), NDA No. 21-612, and a statement has been filed with the Food and Drug Administration ("FDA"), for CIP-FENOFIBRATE (fenofibrate capsules 50 mg, 100 mg, 150 mg, and 160 mg). This NDA includes a "paragraph IV certification" alleging that U.S. Patent Nos. 4,895,726 (expiration date January 19, 2009) (the '726 patent), 6,074,670 (expiration date January 9, 2018) (the '670 patent), and 6,277,405 (Expiration date January 19, 2018) (the '405 patent), will not be infringed by the manufacture, use, or sale of Cipher's fenofibrate capsules that are the subject of the NDA. This notification sets forth a detailed statement of the factual and legal bases for Cipher's opinion that these patents will not be infringed.

I. The Facts

A. The Cipher Product and Process

The Cipher Product is a gelatine capsule containing fenofibrate. This product is prepared by the Cipher Process, namely, melting and blending at 80 degrees centigrade polyglyceride (Gelucire 44/14) and PEG 8,000 and 20,000, then adding fenofibrate to the hot mixture and mixing until the fenofibrate is dissolved. The Cipher Process also involves adding hydroxypropylcellulose and sodium starch glycollate and maintaining the mixture at 75 degrees centigrade. This molten mixture is filled in a liquid state into hard gelatine capsules, and when cooled sets as a "paste" in the capsule. Further details are set forth in U.S. Patent No. 5,545,628 to Deboeck et al.

B. '726 Patent

1. The Claims

The '726 patent contains 12 claims; the following three are representative:

1. A therapeutic composition, which is presented in the form of gelatin capsules and which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 μm .

8. A method for the manufacture of a therapeutic composition according to claim 1 which comprises:
 - (i) intimately mixing and then co-micronizing the fenofibrate and a solid surfactant,

- (ii) adding lactose and starch to the mixture obtained,
- (iii) converting the whole to granules in the presence of water,
- (iv) drying the granules until they contain no more than 1% of water,
- (v) grading the granules,
- (vi) adding polyvinylpyrrolidone and magnesium stearate, and
- (vii) filling gelatine capsules.

10. A method for improving the bioavailability of fenofibrate *in vivo*, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 μm .

2. Analysis

Each of the above claims requires that fenofibrate be co-micronized with a surfactant. The Cipher Product does not contain, and the Cipher Process does not include, micronized fenofibrate alone or in combination with another ingredient. Because the Cipher Process involves melting fenofibrate, no particles of fenofibrate are present in the Cipher Product.

Claims 2, 3, 4, 6, 7 and 8 depend from, and contain all the limitations of claim 1, including the requirement for micronized fenofibrate. Additionally, claim 2 requires a specific ratio of surfactant to fenofibrate, which is absent from the Cipher Product. Claim 4 additionally requires the product to contain sodium lauryl-sulfate, and claim 5 prescribes a specific amount of sodium lauryl-sulfate. The Cipher Product does not contain sodium lauryl-sulfate. Claim 6 requires the mean particle to be of a specific size. As noted above, the Cipher Product contains no particles. Claim 11 depends from, and contains all the limitations of claim 6, although it is directed to a method of treatment. Claim 12 depends from claim 11 and further requires a specific particle size of the active ingredient. Particles of any size are absent from the Cipher Product. Claim 7 further

requires the presence of excipients such as dispersants, fillers and flow enhancers, none of which are present in the Cipher Product. Claim 8 is directed to a method of producing the composition of claim 1 and step (i) is directed to co-micronizing fenofibrate and a solid surfactant. As noted above, the Cipher Process does not involve micronized fenofibrate alone or in combination with another product. Claim 9, depends from claim 8 and further prescribes a specific particle size, a limitation not present in the Cipher Product.

Claim 10, which is independent, has the same recitations of claim 1 except that it is directed to a method of improving bioavailability of fenofibrate *in vivo*. Namely, it recites co-micronizing fenofibrate and a solid surfactant to produce particles of a specific size, all of which are absent from the Cipher Product and Cipher Process.

C. The '670 Patent

1. The Claims

The '670 patent has 38 claims. The independent claims are as follows:

1. An immediate-release fenofibrate composition comprising:
 - (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm , a hydrophilic polymer and a surfactant; and
 - (b) optionally one or several outer phase(s) or layer(s), wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

12. An immediate-release fenofibrate composition comprising:

- (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20µm, polyvinylpyrrolidone, and a surfactant; and
- (b) optionally one or several outer phase(s) or layer(s), and wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said polyvinylpyrrolidone makes up from 25 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight, and wherein fenofibrate and the surfactant are co-micronized.

2. Analysis

Claims 1 and 12 are both directed to immediate release fenofibrate compositions in which the fenofibrate is *in micronized form*. "Micronized form" is defined in the specifications as "a substance in a particulate form, the dimensions of the particle being less than or equal to about 20 µm". Column 3, lines 65-57. The Cipher Product does not contain micronized fenofibrate and does not contain particles in dimensions which are less than or equal to about 20 µm.

During prosecution of the '670 patent, the Examiner cited U.S. Patent No. 5,545,628 by Deboeck, which describes and is specifically directed to the Cipher Product. The patentee carefully distinguished its claimed, micronized product from the "molten solution" of Deboeck (Response of November 17, 1999, page 5, emphasis in original). Thus, a reviewing court would not likely interpret "micronized" as including or being the equivalent of "molten" because the patentee admitted in the record that these two conditions were not the same.

Claims 1 and 12 also require that the composition comprise (1) an inert hydrosoluble carrier that is (2) covered with at least one layer. An "inert hydrosoluble carrier" is defined in the patent as:

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 micron.

This description requires the carrier to be in particulate form and preferably in a particular size range. The Cipher Process involves melting the ingredients together. Thus, none of the ingredients in the Cipher Product are particles.

The specification describes the layer as being "sprayed on." For instance, it states that the invention employs "a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier." Column 2, lines 16-19 (emphasis added). The specification also states that "[t]he composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form ...onto the inert core". This language excludes the possibility that "covered" and "layer" means "mixed in" and "dissolved into" to form a unified compound. Thus, the Cipher Product fails to contain this element of these claims.

Claims 2 to 11 depend from claim 1 and therefore contain all the limitations of claim 1. Additionally, claim 2 prescribes that the composition of claim 1 have a specific dissolution profile. This dissolution profile is the basis for the patentees

claiming an "immediate release" composition. The Cipher Product has a different dissolution profile.

Claim 3 also prescribes that the composition contain polyvinylpyrrolidone (PVP). The Cipher Product does not use PVP. Claim 4 also requires the presence of co-micronized fenofibrate and a surfactant, elements which are missing from the Cipher Product which does not contain micronized ingredients of any type. Claims 5 and 6 require sodium lauryl sulfate, which is absent from the Cipher Product. Claim 11 requires that the hydrosoluble carrier comprise particles of a particular size, elements that are missing from the Cipher Product.

Independent Claim 12 contains all the limitations of Claim 1(a) but is narrower by claiming polyvinylpyrrolidone (PVP) instead of a "hydrophilic polymer". The Cipher Product does not contain PVP.

Claims 13 and 14 depend from and therefore contain all the limitations of Claim 12. Additionally, claim 13 requires sodium lauryl sulfate, which is absent from the Cipher Product, and claim 14 recites a specific dissolution profile which is different from the Cipher Product's dissolution profile.

Claims 15-21 and 35-38 relate to tablets. The Cipher Product is a capsule, not a tablet.

Claim 22 is directed to the process of preparing a composition according to Claim 1 comprising the steps of: (a) preparing a fenofibrate suspension in micronized form in a solution of hydrophilic polymer and surfactant; (b) applying the suspension to an inert hydrosoluble carrier; and (c) optionally coating granules thus obtained with one of several phases or layers. The Cipher Process does not involve any of these three steps.

Claims 23 and 24 depend from and contain all the limitations of claim 22.

Claims 25 to 28 and 31-34 are dependent claims that are directed to capsule formulations. Although the Cipher Product is a capsule formulation, the Cipher Product does not contain the elements recited in the base claims, which have been discussed above. Namely, claim 25 contains all the limitations of claim 1, claim 26 contains all the limitations of claim 6, claim 27 contains all the limitations of claim 12, and claim 28 contains all the limitations of claim 14. Claim 31 has all the limitations of claim 2; claim 32 has all the limitations of claim 4; claim 33 depends from claim 29, which depends from claim 4; and claim 34 depends from claim 30, which depends from claim 6. Additionally, all of these claims recite granules and the Cipher Product does not contain granules.

Claim 29 contains all the limitations of claim 4, which requires the co-micronization of fenofibrate and a surfactant. The Cipher Product does not contain micronized fenofibrate alone or in combination with a surfactant.

Claim 30 contains all the limitations of claim 6, which requires the co-micronization of fenofibrate with sodium lauryl sulfate. The Cipher Product contains no micronized ingredients and no sodium lauryl sulfate.

D. The '405 Patent

1. The Claims

The '405 patent has 13 claims. The only independent claim is as follows:

1. A composition comprising a hydrosoluble carrier and micronized 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 with 0.025M sodium lauryl sulfate.

2. Analysis

The '670 patent and '405 patent share the same specification and are related by virtue of the fact that the '405 patent is a continuation of the '670 patent.

Claim 1 of the '405 patent covers a composition comprising "micronized fenofibrate." The term "micronized" is defined in the specifications as "a substance in a particulate form, the dimensions of the particle being less than or equal to about 20 μm ." Column 4, lines 18-20. The Cipher Product does not contain micronized fenofibrate and does not contain particles in dimensions which are less than or equal to about 20 μm .

Importantly, during prosecution, the Examiner cited a U.S. Patent No. 5,545,628 by Deboeck that describes and is specifically directed to the Cipher Product. The patentee carefully distinguished its claimed, micronized product from the composition of Deboeck:

[T]he presently claimed invention comprises a micronized fenofibrate while Deboeck does not require any particular particle size (Deboeck at column 2, lines 40-42). In fact, Deboeck seeks to avoid micronization (Deboeck at column 2, lines 4-7). Accordingly Deboeck teaches away from the presently claimed micronized fenofibrate.

Response of January 26, 2001, page 7.

The language of Deboeck at column 2, lines 4-7, cited above by the patentee states that:

The present invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is soluble, where by particle size specifications are not required. Emphasis added.

Moreover, in the '670 patent, which is the parent of the '405 patent, as noted above, the patentee carefully distinguished "micronized" from the "molten solution" of Deboeck (Response of November 17, 1999, page 5, emphasis in original). The prosecution history of the '670 patent is highly relevant to the claim interpretation of the '405 patent. The '670 patent is the parent of the '405 patent and contains the same specification as the '405 patent. Both patents contain claims covering micronized fenofibrate compositions. Moreover, the '670 and '405 patents were examined by the same primary examiner and assistant examiner at the U.S. Patent Office. Based on the patentee's arguments over Deboeck in both the '405 patent prosecution and in the '670 patent prosecution, a reviewing court should not interpret "micronized" as including or being the equivalent of "molten."

Claim 1 also recites a "hydrosoluble carrier." As noted above, the specification describes the hydrosoluble carrier as being in particulate form. The Cipher Product does not have any ingredients in particulate form. The various ingredients are mixed and melted together.

Claim 2 depends from claim 1 and therefore contains all of the limitations of claim 1. Claim 2 further requires that the composition be "under the form of a tablet." The form of the Cipher Product is a capsule and not a tablet..

Claim 3 depends from claim 1 and therefore contains all of the limitations of claim 1. Claim 3 further requires that the composition be "under the form of granules

inside a capsule." The Cipher Product is in the form of a molten paste in a capsule not granules.

Claim 4 depends from claim 1 and therefore contains all of the limitations of claim 1. Claim 4 further requires that the micronized fenofibrate have a size less than or equal to 20 μm . As stated above, the Cipher Product does not contain micronized fenofibrate particles of a size less than or equal to 20 μm .

Claim 5 depends from claim 4 and therefore contains all the limitations of claim 4. Claim 5 further specifies a smaller fenofibrate particle size, i.e., of less than or equal to 10 μm . Again, the Cipher Product does not contain particles of fenofibrate.

Claim 6-13 either directly or indirectly depend from claim 1 and therefore contains all of the limitations of claim 1 and therefore require elements not present in the Cipher Product.

II. The Legal Basis for Non-Infringement

Under U.S. law, a court would first interpret the scope and meaning of patent claims and then compare the properly construed claims to the allegedly infringing product. The absence of even one claim element avoids literal infringement. Therefore, to establish literal infringement, every limitation set forth in a claim must be found in the accused product.

In each of the above patents, the claims must be interpreted as containing fenofibrate in a specific form, *i.e.* in *micronized form*. The independent claims recite this limitation and the dependent claims incorporate such limitation by virtue of dependency. Because the Cipher Process does not involve micronization of any of the fenofibrate alone or in combination with another ingredient, and the Cipher Product does not in fact contain micronized ingredients, this element is absent and the Cipher Product and Cipher Process, which therefore avoid literal infringement. However, as pointed out above in the claim by claim analysis, other elements in various independent and dependent claims are also absent from the Cipher Product thereby providing further bases for voiding infringement.

Even where no literal infringement exists, a product may nevertheless infringe a patent under the doctrine of equivalents, which permits a court to extend the effective scope of patent protection beyond a claim's literal wording. However, even under the doctrine of equivalents, each element or equivalent of such element in a claim must be present. It is clear from the above claim by claim analysis that the Cipher Product fails to contain many of the elements in the claims. For instance, in the '670 patent, there is a requirement that the composition have a carrier that is actually covered with fenofibrate. This feature or an equivalent thereof is totally absent from the Cipher Product.

More importantly, however, is the fact that with regard to all of the claims in each of the above patents, is the effect of prosecution history estoppel. That is, the

patentee, in each patent, relied upon the micronization feature of their invention to obtain allowance of the claims. In the '670 and '405 patent file histories, the patentee actually distinguished micronization over the melting process used by Cipher. In the '726 patent, the patentees stressed throughout their specification how the co-micronization of fenofibrate with a solid surfactant had a synergistic effect on the bioavailability of the active ingredient. In view of such statements and arguments, it is doubtful that a reviewing court would expand the scope of the micronization feature of the claims to including "melting."

Therefore, the Cipher Product and Cipher Process avoid literal infringement and infringement under the doctrine of equivalents of all of the claims in each of the '726, '670 and '405 patents.

As a courtesy, I enclose the three patents listed in the FDA Orange Book (# 4,895,726, 6,047,670 and 6,277,405, and the Deboeck patent # 5,545,628.

I also enclose Cipher Pharmaceuticals U. S. Agent address and telephone and facsimile numbers.

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