DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Cipher Pharmaceuticals Inc.
Attn: Arthur M. Deboeck, Vice President and General Manager
Galephar Pharmaceutical Research Inc. [US Agent for Cipher Pharmaceuticals Inc.]
Road 198 Km 14.7 #100 Juncos Industrial Park
Juncos, PR 00777-3873

RE: NDA 21612
LIPOFEN® (fenofibrate capsules, USP) for oral use
MA #128

Dear Mr. Deboeck:

This letter notifies Cipher Pharmaceuticals Inc. (Cipher) that as part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed an "e-Pharm/alert" email (LIP-TR-0025) (email) for LIPOFEN® (fenofibrate capsules, USP) for oral use (Lipofen). This email is false or misleading because it makes unsubstantiated superiority claims. Thus the email misbrands Lipofen within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a), (n); 331(a). *See* 21 CFR 202.1(e)(6)(ii).

Background

Below are the indications and summary of the most serious and most common risks associated with the use of Lipofen.[1] According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (in pertinent part):

> LIPOFEN is indicated as adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-c), Triglycerides (TG) and apolopoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia.
>
> LIPOFEN is also indicated as adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacologic intervention.
>
> Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Important Limitations of Use
Fenofibrate at a dose equivalent to 150 mg of LIPOFEN was not shown to reduce coronary heart disease morbidity and mortality in 2 large, randomized controlled trials of patients with type 2 diabetes mellitus.

Lipofen is contraindicated in nursing mothers and in patients with severe renal impairment, active liver disease, preexisting gallbladder disease, and known hypersensitivity to fenofibrate or fenofibric acid. The PI also contains Warnings and Precautions regarding coronary heart disease morbidity and mortality, myopathy and rhabdomyolysis, coadministration with coumarin anticoagulants, pancreatitis, hematologic changes, venothromboembolic disease, and paradoxical decreases in HDL cholesterol levels.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The email includes the following claims and presentations (emphasis original):

- "**e-Pharm/alert: All fenofibrates are not created equal**" (email subject line)

- "**When a patient is prescribed LIPOFEN® (fenofibrate capsules, USP), a generic fenofibrate may not be the best option. Only LIPOFEN offers Lidose® technology, which:**

    - Uses a unique lipid melt matrix system not available with any other generic or brand-name fenofibrate[2,3,4]
    - Delivers reliable, consistent, and uniform delivery[2,3]
    - Avoids dependence on particle formulation[2]
    - May improve the safety and efficacy of the active ingredient in LIPOFEN by offering more consistent plasma profiles."[3]

[2] Food and Drug Administration Web site—Cipher Pharmaceuticals Limited. 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. Available at: http://www.fda.gov/ohrms/dockets/dockets/04p0386/04p-0386-cp00001-Exhibit-04-French-vol1.pdf. Accessed May 7, 2013.
[3] Laboratoires S.M.B. Web site. Lidose. http://www.smblab.be/index.php/formulation/lidose. Accessed May 7, 2013.
[4] United States Patent and Trademark Office Web site. Pharmaceutical composition containing fenofibrate—Patent 5,545,628. Available at: http://patft.uspto.gov. Accessed May 7, 2013.

- "**LIPOFEN Takes Particle Size Out of the Equation**"[4]
  (Accompanied by a depiction of scan images comparing an "Ordinary Fenofibrate" with "LIPOFEN With Lidose")

    - "Other fenofibrates are formulated with small particles, which may affect absorption[3]
      — With LIPOFEN, particle size is not an issue[4]
    - Fenofibrate is in an already-dissolved state, making it readily available for absorption[4]
    - LIPOFEN with Lidose technology offers a very homogeneous distribution of fenofibrate in the mass of excipients[3]
      — No crystals of fenofibrate are observed"[3]

The totality of these claims and presentations misleadingly implies that Lipofen offers a clinical advantage over other available fenofibrate products, as a result of its formulation and delivery system, when this has not been demonstrated by substantial evidence. There are several references cited[2,3,4] in support of the claims and presentations. The Notice of Paragraph IV Certification[2], the SMB website[3], and the U.S. patent document[4] include descriptive information regarding Lidose® technology and a product patent. However, none of the cited references describe any clinical trial data comparing Lipofen to other fenofibrate products to support claims of superiority. In general, claims of superiority must be supported by adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drugs. Therefore, the references cited do not support the suggestion that Lipofen is superior to other fenofibrate products. In addition, FDA is not aware of any head-to-head clinical trials comparing Lipofen to other fenofibrate products, or any evidence to support the claims that Lipofen's "Lidose" technology provides a clinical advantage over other fenofibrate products. Lipofen was approved as a 505(b)(2) application demonstrating its bioequivalence, not its superiority, to TRICOR® (fenofibrate tablets). According to the CLINICAL PHARMACOLOGY section of the PI, "The extent and rate of absorption of fenofibric acid after administration of 150 mg LIPOFEN capsules are equivalent under low-fat and high-fat fed conditions to 160 mg TriCor® tablets." Although we acknowledge that some of the above claims may be true; the totality of the claims and presentations misleadingly implies that Lipofen offers a clinical advantage over other fenofibrate products.

Conclusion and Requested Action

For the reasons discussed above, the email misbrands Lipofen within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a), (n); 331(a). *See* 21 CFR 202.1(e)(6)(ii).

OPDP requests that Cipher immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before September 26, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Lipofen that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #128 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Lipofen comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Adora Ndu, Pharm.D.
Team Leader
Office of Prescription Drug Promotion

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

/s/

ANKUR S KALOLA
09/11/2014

ADORA NDU
09/11/2014