



NDA 50824

LABELING ORDER

GastroEntero-Logic, LLC
Attention: Lewis Tepper
President, Regulatory Affairs
400 Kelby Street, Parker Plaza 10th Floor
Fort Lee, NJ 07024

Dear Mr. Tepper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Omeclamox-Pak (Omeprazole/clarithromycin/amoxicillin).

On October 31, 2014, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Omeclamox-Pak (Omeprazole/clarithromycin/amoxicillin) to address the risk of concomitant dosing of mycophenolate mofetil with proton pump inhibitors (PPIs) resulting in reduced systemic exposure of mycophenolate mofetil as reported in current literature. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

The 30 days have passed and we have not received any submission from you addressing our letter dated October 31, 2014.

You failed to respond to our October 31, 2014, letter within 30 days. Under the authority of Section 505(o)(4)(E), we are ordering you to make all of the changes in the labeling listed in the October 31, 2014, letter (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the October 31, 2014, letter must be received by FDA by December 30, 2014 for Omeclamox-Pak (Omeprazole/clarithromycin/amoxicillin).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by December 20, 2014, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level."

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf>. The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 22, Room 6468
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Susmita Samanta
Safety Regulatory Project Manager
Food and Drug Administration
Division of Anti-Infective Products
Building 22, Room 6152
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, “Formal Dispute Resolution: Appeals Above the Division Level” for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Khushboo Sharma, CDER Formal Dispute Resolution Project Manager, at (301) 796-0700. Appeals received by the Agency later than December 20, 2014, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to \$250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, call Susmita Samanta, Safety Regulatory Project Manager, at (301) 796-0803.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Safety Labeling Change Notification Letter



NDA 50824

SAFETY LABELING CHANGE NOTIFICATION

Dava Pharmaceuticals, Inc.
Attention: Susan Hamet
Vice President, Regulatory Affairs
400 Kelby Street, Parker Plaza 10th Floor
Fort Lee, NJ 07024

Dear Ms. Hamet:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Omeclamox-Pak (Omeprazole/clarithromycin/amoxicillin).

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Omeclamox-Pak (Omeprazole/clarithromycin/amoxicillin) was approved on February 8, 2011, we have become aware of the risk of concomitant dosing of mycophenolate mofetil with proton pump inhibitors (PPIs) resulting in reduced systemic exposure of mycophenolate mofetil as reported in current literature.

We consider this risk to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for the class of drugs containing a PPI component as follows (underlining indicates an ADDITION, ~~strike through~~ indicates a DELETION):

HIGHLIGHTS

Drug Interactions

- Omeprazole may interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, ampicillin esters, ^{(b) (4)}-digoxin, and mycophenolate mofetil).

FULL PRESCRIBING INFORMATION

7.0 DRUG INTERACTIONS

7.15 Drugs for Which Gastric pH Can Affect Bioavailability

~~OMEPRAZOLE DELAYED-RELEASE CAPSULES, USP, 20 mg, CLARITHROMYCIN TABLETS, USP, 500 mg, and AMOXICILLIN CAPSULES, USP, 500 mg, may interfere with the absorption of drugs for which gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts) because of its inhibition of gastric acid secretion by the omeprazole component of OMEPRAZOLE DELAYED-RELEASE CAPSULES, USP, 20 mg, CLARITHROMYCIN TABLETS, USP, 500 mg, and AMOXICILLIN CAPSULES, USP, 500 mg.~~

Due to its effects on gastric acid secretion, omeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. As with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil can decrease, while the absorption of drugs such as digoxin can increase during treatment with omeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Coadministration of digoxin with omeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with omeprazole.

Coadministration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the exposure to mycophenolic acid (MPA), the active moiety, possibly due to a decrease in MPA solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors (PPIs) and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil [See Clinical Pharmacology (12.3)].

12.3 Pharmacokinetics (Please add mycophenolate mofetil following the *Voriconazole and Omeprazole* paragraph)

Mycophenolate mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of mycophenolate mofetil approximately one hour after the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the C_{max} and 23% reduction in the AUC of mycophenolic acid.

We have also determined that the labeling changes listed below are warranted for your product:

The risk of acute interstitial nephritis (AIN) should be added to the Warnings and Precautions section of the package insert.

HIGHLIGHTS

Recent Major Changes

Acute Interstitial Nephritis (5.6) 11/2014

Warnings and Precautions

- Acute interstitial nephritis has been observed in patients taking PPIs. (5.6)

FULL PRESCRIBING INFORMATION

5.0 WARNINGS AND PRECAUTIONS

5.6 Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue omeprazole if AIN develops. [see Contraindications (4.1)]

Sections 5.6 through 5.8 in the last approved labeling should be renumbered as sections 5.7 through 5.9 in the proposed labeling, and the table of contents should be revised accordingly.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above directions, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT**

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, call Susmita Samanta, Safety Regulatory Project Manager, at (301) 796-0803.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

SUMATHI NAMBIAR
10/31/2014

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/s/

EDWARD M COX
12/15/2014