DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

October 11, 2006

Jean-Jacques Bienaimé
Chief Executive Officer
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Re: ANDA # 75-117
Orapred® (prednisolone sodium phosphate oral solution)
MACMIS ID # 13850

WARNING LETTER

Dear Mr. Bienaimé:

This letter notifies BioMarin Pharmaceutical Inc. (BioMarin), and by copy, Alliant Pharmaceuticals, Inc. which markets Orapred® (prednisolone sodium phosphate oral solution) (Orapred) on behalf of BioMarin, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a product website (http://www.orapredsmallpackage.com) (ORA05050) for Orapred® (prednisolone sodium phosphate oral solution) (Orapred) submitted by BioMarin under cover of Form FDA 2253. The product website is misleading in that it minimizes and fails to communicate risk associated with the use of Orapred, broadens the indication for Orapred, and makes unsubstantiated claims. Thus, the product website misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§352(a) & (n), 321(n), and FDA's implementing regulations. *See* 21 CFR 202.1(e)(3)(i); (e)(5)(i); (e)(5)(iii) & (e)(6)(i). Your product website raises significant public health and safety concerns because it suggests that Orapred is safer and more effective than has been demonstrated.

Background

According to its FDA-approved product labeling (PI), Orapred is indicated in a variety of conditions, including the following (in pertinent part):

> **1. Allergic States**
> **Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adult and pediatric populations with:** seasonal or perennial allergic rhinitis; **asthma**; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions. (emphasis added)
>
> ....

10. Respiratory Diseases
Symptomatic sarcoidosis; idiopathic eosinophilic pneumonias; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; **asthma (as distinct from allergic asthma listed above under "Allergic States")**, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, acute exacerbations of chronic obstructive pulmonary disease (COPD), and Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV (+) individual who is also under treatment with appropriate anti-PCP antibiotics. Studies support the efficacy of systemic corticosteroids for the treatment of these conditions: allergic bronchopulmonary aspergillosis, idiopathic bronchiolitis obliterans with organizing pneumonia....(emphasis added).

The PI for Orapred reflects important contraindications, warnings - including a bolded warning - precautions, and adverse reactions, as discussed in part below:

Contraindications

According to the Contraindications section, Orapred is contraindicated in patients with systemic fungal infections.

Warnings

"Vaccination: Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered, however, the response to such vaccines can not be predicted...."

Precautions

According to the Neuro-psychiatric section, Orapred may cause mood swings.

Adverse Reactions

Adverse effects of Orapred include the following: endocrine (including development of cushingoid state, increased requirements for insulin or oral hypoglycemic agents in diabetic patients, manifestations of latent diabetes mellitus); fluid and electrolyte disturbances (including fluid retention, hypertension); gastrointestinal (including peptic ulcer with possible perforation and hemorrhage); increased appetite; and weight gain.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal material facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The product website makes efficacy claims for Orapred but omits and minimizes risks associated with Orapred. Specifically, the main product website states:

- "Orapred® (prednisolone sodium phosphate oral solution) is a US Food and Drug Administration (FDA) approved oral liquid steroid."

- "Orapred's patented taste masking technology neutralizes prednisolone's unpleasant taste."

In addition, the main product website contains links to numerous other pages that contain claims about Orapred. For example, the link titled "About Orapred" contains the following claims:

- "Orapred® (Prednisolone Sodium Phosphate Oral Solution) For Exacerbations Of Asthma"
- "Orapred is designed to reduce this inflammation and allow asthma patients to breath normally."
- "Designed to taste better and ease administration"
- "Its proprietary taste-masking technology helps mask the bitter taste of prednisolone, making it easier to take without experiencing the natural gag reflex commonly induced by other liquid formulations of prednisolone."

Similarly, the link titled "Contact" contains the following claim:

- "Orapred® (Prednisolone Sodium Phosphate Oral Solution) For Exacerbations Of Asthma"

However, while these pages contain efficacy claims for Orapred, they fail to provide any information on the risks associated with the use of Orapred. While there is a link to the full prescribing information on the second page of the product website, this does not mitigate the misleading omission of risk information from the web pages listed above.

The only risk information about Orapred on the product website is on the "Ordering Information" and "NEW INSTITUTIONAL 10-PACKS" links. These pages include the statement: "As with all glucocorticoids, Orapred is contraindicated in persons with systemic fungal infections. Please see full prescribing information for a complete listing of adverse events such as dermatological and gastrointestinal disturbances." This statement fails to convey important warnings, precautions, and adverse reactions associated with Orapred. See Background section, above. Furthermore, inclusion of the risk information on the "Ordering Information" and "NEW INSTITUTIONAL 10-PACKS" pages does not mitigate the misleading omission of risk information on the web pages listed above.

Broadening of Indication/Failure to State Full Indication

According to the Indications and Usage section of the PI, Orapred is indicated for the control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adult and pediatric populations with asthma or asthma caused by respiratory disorders. The product website contains a general discussion of asthma triggers and treatment that misleadingly implies that Orapred is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. For example, the following claims from the product website misleadingly fail to disclose the important limitations to Orapred's indication:

- "Individuals with asthma experience an inflammation that causes the airways to constrict, making breathing difficult. Orapred is designed to reduce this inflammation and allow asthma patients to breathe normally." ("About Orapred" page on the product website)
- "Orapred® (Prednisolone Sodium Phosphate Oral Solution) For Exacerbations Of Asthma" ("About Orapred" and "Contact" pages on the product website)

Unsubstantiated Claims

The "NEW INSTITUTIONAL 10-PACKS" link on the main product website claims that Orapred is "ENGINEERED FOR COMPLIANCE," and the main product website contains the tagline, "Perfecting the Science of Compliance." Similarly, the "About Orapred" page on the product website claims that Orapred "helps mask the bitter taste of prednisolone, making it easier to take without experiencing the natural gag reflex commonly induced by other liquid formulations of prednisolone." In addition, the "NEW INSTITUTIONAL 10-PACKS" link on the main product website contains claims such as, "Designed to taste better, ease administration." We acknowledge that Orapred contains flavor enhancers. However, these claims misleadingly suggest that because of its formulation, patients gag less often when taking Orapred or that the taste of Orapred is superior to that of other formulations of prednisolone and thus that Orapred improves rates of compliance. FDA is not aware of any evidence to support these claims. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the product website misbrands Orapred in violation of the Act and FDA's implementing regulations. 21 U.S.C. §§352(a) & (n); 321(n); *see also* 21 CFR 202.1(e)(3)(i); (e)(5)(i); (e)(5)(iii) & (e)(6)(i).

DDMAC requests that BioMarin immediately cease the dissemination of violative promotional materials for Orapred such as those described above. Please submit a written response to this letter on or before October 24, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Orapred such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 13850 in addition to the ANDA number. We remind 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 Orapred comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas Abrams, RPh, MBA
Division Director
Division of Drug Marketing,
Advertising, and Communications

cc: Mark Hugh
President and CEO
Alliant Pharmaceuticals, Inc.