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TRANSMITTED VIA FACSIMILE

NOV 14 2002

Stefan Antonsson
President
Xanodyne Pharmacal, Inc.
7310 Turfway Road
Suite 490
Florence, KY 41042

Re: **NDA #11-719, 08-107, 15-229**
Methotrexate (methotrexate sodium injection)
Leucovorin (leucovorin calcium injection)
Amicar (aminocaproic acid)
MACMIS ID# 10894

WARNING LETTER

Dear Mr. Antonsson:

This letter notifies Xanodyne Pharmacal, Inc. (Xanodyne) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a brochure (Item XIB-1) for Methotrexate, Leucovorin, and Amicar and accompanying materials that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. The brochure discusses three Xanodyne drugs, Methotrexate, Leucovorin, and Amicar, two of which are also highlighted in an accompanying letter and business reply card. The brochure and accompanying materials tout the usefulness of these agents, but fail to provide any risk information. In addition, the brochure and accompanying materials fail to provide important information on the limitations to the indicated uses of these drugs. We consider this to be an omission of material facts and therefore misleading under Section 201(n) of the Act. Your failure to disclose the serious, sometimes fatal, risks associated with treatment with these agents and the appropriate conditions for their use raises significant public health and safety concerns.

Background

Methotrexate, Leucovorin, and Amicar were approved in 1959, 1952, and 1964, respectively. These agents are indicated for treatment of very specific conditions and are associated with very serious health risks that are sometimes fatal.

Methotrexate is associated with serious toxic reactions that can be fatal. Therefore, this drug should only be used in life threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. Deaths have been reported with the use of methotrexate in the treatment of malignancy. Patients should be monitored for bone marrow, liver, lung, and kidney toxicities. The use of a high dose methotrexate regimen that is recommended for osteosarcoma requires meticulous care. Methotrexate has been reported to cause fetal death and congenital anomalies. Unexpectedly severe, sometimes fatal, bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate along with some nonsteroidal anti-inflammatory drugs. Methotrexate causes hepatotoxicity, fibrosis, and cirrhosis after prolonged use. Methotrexate-induced lung disease, a potentially dangerous lesion, may occur at any time during therapy even with low doses and is not always fully reversible. Therapy must be interrupted for diarrhea and ulcerative stomatitis; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Potentially fatal opportunistic infections may occur with methotrexate therapy. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

There are serious risks associated with Leucovorin treatment as well. When used in the treatment of accidental overdosages of intrathecally administered (introduced into the space under the arachnoid membrane of the brain or spinal cord) folic acid antagonists, Leucovorin should not be administered intrathecally. Leucovorin may be harmful or fatal if given intrathecally. Large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible pediatric patients. Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported with administration of this drug. Anaphylactic reactions, including shock, have been reported. Excessive amounts of Leucovorin may nullify the chemotherapeutic effect of methotrexate, allowing the cancer to progress.

There are also serious risks associated with Amicar treatment. Amicar should not be given when there is evidence of an active intravascular clotting process. In patients with upper urinary tract bleeding, Amicar administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. There are rare reports of skeletal muscle weakness with necrosis of muscle fibers following prolonged administration. Acute overdosages with Amicar administered intravenously have resulted in transient hypotension to severe acute renal failure leading to death.

The brochure at issue was mailed to physicians in an envelope prominently marked with a red box as "NEW PRODUCT INFORMATION." The brochure makes broad efficacy claims for Methotrexate, Leucovorin, and Amicar, as discussed in greater detail below. An

accompanying letter, sent by your Vice-President of Marketing, Richard R. Hendrixson, Ph.D., also highlights Methotrexate and Leucovorin, stating that "in nearly 40 years of clinical experience, these chemotherapeutic agents have established a strong efficacy and safety profile." Also enclosed was a business reply card that highlighted these products as cancer-treatment related agents, solicited physicians to be on Xanodyne's mailing list to receive product information, and asked whether the physician would like to be contacted by a Xanodyne representative. None of these materials presents any risk information about the promoted products. The mailing also did not include the approved product labeling (PI) for any of the promoted products.

Omission of Risk Information

The brochure includes important efficacy claims, such as "Each of these innovator products play a critical role in the treatment of cancer and certain bleeding disorders," "... methotrexate has its maximum effect on cells that are actively reproducing, such as cancer cells," "Leucovorin calcium... can help protect cells from the negative effects of folate-antagonists such as methotrexate," and "Amicar is used in the treatment of certain excessive bleeding disorders." The accompanying letter touts the 40 years of clinical experience with Methotrexate and Leucovorin and claims that "these chemotherapeutic agents have established a strong efficacy and safety profile." There is no reference, however, to risks in any of these materials.

It is particularly concerning that Xanodyne has failed to provide any risk information because each of these drugs has been associated with potentially fatal reactions, as outlined above. For example, Methotrexate's PI includes a boxed warning regarding the possibility of serious toxic, fatal reactions. It notes that "Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis." The PI for Leucovorin includes a warning that Leucovorin must not be administered intrathecally because such administration may be harmful or fatal to patients. The warning in the PI for Amicar states that "In patients with upper urinary tract bleeding, Amicar administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. For this reason, Amicar should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk." By failing to include any of this important risk information, Xanodyne misleadingly suggests that these drugs are safer than has been demonstrated by substantial evidence or substantial clinical experience.

Omission of Material Facts Regarding Approved Indications and Uses

The brochure for Methotrexate, Leucovorin, and Amicar is also misleading because it omits material facts regarding the approved uses of these drugs, as outlined below:

Methotrexate

The brochure includes the claims "Methotrexate is a chemotherapeutic agent that belongs to a group of compounds known as antimetabolites" and "...methotrexate has its maximum effect on cells that are actively reproducing, such as cancer cells" but fails to convey that

Methotrexate is approved for treatment of specific, not all, neoplastic diseases, and only under specific conditions in some diseases. The PI states:

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (Cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Leucovorin

The brochure includes the claim "Leucovorin calcium... can help protect cells from the negative effects of folate-antagonists such as methotrexate" but, again, fails to include substantial limitations regarding the disease being treated and the stage of the disease.

The brochure also fails to provide information regarding the specific use of Leucovorin and Methotrexate. As stated in the respective PI's for Leucovorin and Methotrexate:

Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Amicar

The brochure includes the claim "Amicar is used in the treatment of certain excessive bleeding disorders. It is used as an antifibrinolytic agent that acts to interrupt the process of breaking down fibrin (fibrinolysis)" but fails to convey the limitations of the indication. As stated in the PI for Amicar:

Amicar is useful in enhancing homeostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia; abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the genitourinary system).

By omitting the specific approved indications for Methotrexate, Leucovorin, and Amicar, the brochure misleadingly suggests that these drugs are effective for conditions beyond those that have been approved by the Food and Drug Administration. Similarly, the accompanying letter and business reply card describe Methotrexate and Leucovorin generally as "chemotherapeutic agents" and "cancer-treatment related agents," respectively, but fail to specify the indicated uses for these drugs. Xanodyne also failed to include the PI's for Methotrexate, Leucovorin, or Amicar with the brochure and other materials, in violation of 21 CFR 201.100(c)(2), thus further failing to provide readers with more information about the appropriate use of these drugs and the potential hazards associated with their use.

Failure to Submit Post-Marketing Reports

Our records indicate that Xanodyne has failed to submit these promotional materials at the time of initial dissemination as required under the post-marketing reporting requirements (21 CFR 314.81 (b)(3)(i)).

Conclusions and Requested Actions

You have disseminated a brochure and accompanying materials that fail to provide any risk information and that omit material facts regarding the approved indications and uses for Methotrexate, Leucovorin, and Amicar. Due to the significant public health and safety concerns raised by these materials, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

- 1) Immediately ceasing the dissemination of this brochure, the accompanying letter and business reply card, and all promotional materials that contain the same or similar violations outlined in this letter.

- 2) Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the violative brochure and/or accompanying violative materials.
- 3) Providing a written statement of your intent to comply with "1" and "2" above.

Xanodyne should submit a written response to DDMAC by November 18, 2002, describing its intent and plans to comply with DDMAC's request. If you have any questions or comments, please contact Catherine A. Miller, MT (ASCP), Carol Barstow, JD, or Jean-Ah Kang, PharmD by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10894 in addition to the NDA numbers.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Methotrexate, Leucovorin, and Amicar, and may determine that additional remedial messages will be necessary to fully correct the false and misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Thomas Abrams

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