DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Timothy K. Ressler, MS, MT (ASCP)
Vice President, Regulatory Affairs
MGI PHARMA, Inc.
5775 West Old Shakopee Road
Suite 100
Bloomington, Minnesota 55437-3174

**RE: NDA # 20-637**
**Gliadel® Wafer (polifeprosan 20 with carmustine implant)**
**MACMIS # 14575**

Dear Mr. Ressler:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a journal advertisement (GL0014) (journal ad) for Gliadel Wafer (polifeprosan 20 with carmustine implant) (Gliadel Wafer) submitted by MGI PHARMA, Inc. (MGI) under cover of Form FDA 2253. This two-page promotional piece is misleading because it fails to disclose the full indication and presents unsubstantiated claims regarding Gliadel Wafer. The journal ad therefore misbrands the drug in violation of Sections 502(n) and 201(n) of the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. §§ 352(n) & 321(n) and FDA implementing regulations, 21 CFR 202.1(e)(3)(ii) and 202.1 (e)(6)(i).

## Background

As stated in the Indication and Usage section of the approved product labeling (PI), "Gliadel Wafer is indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. Gliadel Wafer is [also] indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery."

The indication for newly-diagnosed high-grade malignant glioma patients is based on a randomized, double-blind, placebo-controlled clinical trial that was conducted in two hundred and forty adult patients with newly-diagnosed high-grade malignant glioma undergoing initial craniotomy for tumor resection. This trial was designed to determine the safety and efficacy of Gliadel Wafer implants plus surgery and radiation therapy compared to placebo implants plus surgery and radiation. Patients were followed for at least three years or until death. The median survival increased from 11.6 months with placebo to 13.9 months with Gliadel Wafer (p-value <0.05, log-rank test). The hazard ratio for Gliadel Wafer treatment was 0.73 (95% CI: 0.56-0.95) in this study population.

**Failure to Disclose the Full Indication**

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made. This promotional piece is misleading because it includes efficacy and safety data for patients implanted with Gliadel Wafer during initial craniotomy, but fails to present the corresponding approved indication for Gliadel (i.e., Gliadel Wafer is indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation). See 21 CFR 202.1(e)(3)(ii).

**Unsubstantiated Claims**

The promotional piece states, "TAKE THE PATH TO AVOID TREATMENT DELAYS," "GLIADEL WAFER WORKS AT DAY 1," "Cells may double after 10 days…," and "Only 1 therapy…that avoids treatment delays post surgery." The totality of this presentation suggests that Gliadel Wafers' particular advantage, compared to radiation therapy alone, is avoidance of treatment delay. These claims further imply that early use of Gliadel Wafers provides a clinical benefit during the fourteen days from implantation to initiation of traditional radiation therapy, and represents the basis for its effectiveness. While FDA acknowledges that Gliadel Wafer has demonstrated a survival benefit compared to radiation alone, FDA is not aware of any evidence that the efficacy of Gliadel Wafer results from the ability to use the Gliadel Wafer at the time of surgery.

In the controlled clinical study used to support the approval of this NDA, Gliadel Wafers or placebo wafers were implanted during craniotomy for tumor resection, and the majority of patients received a standard course of radiotherapy, typically starting 3 weeks after surgery. The timing of Gliadel Wafer implantation in this study was based on necessity (i.e., implantation requires craniotomy) rather than any known benefit from treating immediately after surgery. The "delay" in the treatment of glioma between surgery and the beginning of radiotherapy was merely the prescribed time to allow for necessary healing after surgery. FDA is unaware of any substantial evidence to support MGI's claims implying that the timing of Gliadel Wafer implantation prior to radiotherapy provides a clinical benefit (e.g., "TAKE THE PATH TO AVOID TREATMENT DELAYS" and "Only 1 therapy…that avoids treatment delays post surgery") or that, in the absence of early Gliadel Wafer implantation, there is a potential for significant disease progression during the period prior to radiotherapy (e.g., "Cells may double after 10 days…"). Furthermore, the reference[1] cited in the promotional piece to support the latter claim regarding tumor size is from an *in vitro* labeling study utilizing a new method for calculation of the "potential doubling time" of glioma cells which does not represent substantial evidence. These *in vitro* data are not an adequate basis to predict the effectiveness of Gliadel Wafers on cell growth following cranial implantation.

MGI further states "GLIADEL WAFER WORKS AT DAY 1" and provides two references[2,3] in support of the claim. FDA finds that this claim is misleading because the references discuss rat and monkey studies—not human studies. Moreover, these animal studies do not

[1] Matsutani M. Cell kinetics. In: Berger MS, Wilson CB, eds. The Gliomas. Philadelphia, Pa: WB Saunders Co; 1999:204-209.
[2] Fung LK, Shin M, Tyler B, Brem H, Saltzman WM. Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. *Pharm Res.* 1996 May;13(5):671-82.
[3] Fung LK, Ewend MG, Sills A, Sipos EP, Thompson R, Watts M, et al. Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Res.* 1998 Feb 15;58(4):672-84.

measure the time to actual glioma cell death in humans. Instead, these studies reported on the release of carmustine (from implanted Gliadel Wafers), which is taken up by surrounding brain tissues including residual glioma. FDA is unaware of substantial evidence to support MGI's extrapolation that this carmustine uptake results in immediate glioma cell death or when actual glioma cell death occurs following Gliadel Wafer implantation.

**Conclusion and Requested Action**

The promotional piece is misleading because it fails to disclose the full indication that corresponds to the claims for Gliadel Wafer presented in the piece and presents unsubstantiated claims for Gliadel Wafer. Therefore, it misbrands the drug in violation of the Act and FDA implementing regulations. See 21 U.S.C. §§ 352(n) & 321(n) and 21 CFR 202.1(e)(3)(ii) and 202.1(e)(6)(i).

DDMAC requests that MGI immediately cease the dissemination of promotional materials for Gliadel Wafer the same as or similar to those described above. Please submit a written response to this letter on or before February 9, 2007, describing your intent to comply with this request, listing all promotional materials for Gliadel Wafer that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of these 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, or by facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 14575 in addition to the NDA 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 Gliadel Wafer comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

*{See appended electronic signature page}*

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

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/s/

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Joseph Grillo

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