DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Louise Peltier
Senior Director, Regulatory Affairs
Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

Re: NDA #20-637
Gliadel Wafer (polifeprosan 20 with carmustine implant)
MACMIS ID # 11459

Dear Ms. Peltier:

This letter notifies Guilford Pharmaceuticals Inc. (Guilford) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has received a video tape ("the video tape") titled, "Treatment Options for Malignant Gliomas: David M. Bailey Interviews Allan J. Hamilton, MD" (SP01024) for Gliadel Wafer (polifeprosan 20 with carmustine implant), submitted by Guilford with Form FDA 2253 (advertisements and promotional labeling), that is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and applicable regulations. It appears that the video tape is provided by Guilford to physicians for dissemination to patients. Specifically, the video tape omits material risk information and overstates the efficacy of Gliadel Wafer in violation of Sections 502(a) and 201(n) of the Act. Our specific objections follow:

Omission of Material Risk Information

The video tape misleadingly omits material regarding significant risks associated with Gliadel Wafer. This omission minimizes the risks of Gliadel Wafer and misleadingly suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. As stated in the approved product labeling (PI):

> "Patients undergoing craniotomy for malignant glioma and implantation of Gliadel (polifeprosan 20 with carmustine implant) should be monitored closely for known complications of craniotomy, including seizures, intracranial infections, abnormal wound healing, and brain edema. Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with Gliadel, including one case leading to brain herniation.
>
> "Carmustine, the active component of Gliadel, can cause fetal harm when administered to a pregnant woman.

"Communication between the surgical resection cavity and the ventricular system should be avoided to prevent the wafers from migrating into the ventricular system and causing obstructive hydrocephalus.

"Computed tomography and magnetic resonance imaging of the head may demonstrate enhancement in the brain tissue surrounding the resection cavity after implantation of Gliadel Wafers (polifeprosan 20 with carmustine implant). This enhancement may represent edema and inflammation caused by Gliadel or tumor progression.

"The short and long-term toxicity profiles of Gliadel when given in conjunction with radiation or chemotherapy have not been fully explored.

"The following four categories of adverse events are possibly related to treatment with Gliadel Wafer (polifeprosan 20 with carmustine implant).

1. Seizures: In the randomized study, the majority of seizures in the placebo and Gliadel groups were mild or moderate in severity…. The median time to onset of the first new or worsened post-operative seizure was 3.5 days in patients treated with Gliadel and 61 days in placebo patients.

2. Brain Edema: In the randomized trial, brain edema was noted in 4% of patients treated with Gliadel and in 1% of patients treated with placebo. Development of brain edema with mass effect (due to tumor recurrence, intracranial infection, or necrosis) may necessitate re-operation and, in some cases, removal of wafer or its remnants.

3. Healing Abnormalities: The majority of these events were mild to moderate in severity. Healing abnormalities occurred in 14% of Gliadel-treated patients compared to 5% of placebo recipients. These events included cerebrospinal fluid leaks, subdural fluid collections, subgaleal or wound effusions, and wound breakdown.

4. Intracranial Infection: In the randomized trial, intracranial infection (meningitis or abscess) occurred in 4% of patients treated with Gliadel and in 1% of patients receiving placebo. In Gliadel-treated patients, there were two cases of bacterial meningitis, one case of chemical meningitis, and one case of meningitis which was not further specified. A brain abscess developed in one placebo-treated patient. The rate of deep wound infection (infection of subgaleal space, bone, meninges, or neural parenchyma) was 6% in both Gliadel and placebo treated patients."

In the video tape, Dr. Hamilton addresses the complications and adverse effects of Gliadel Wafer use, only mentioning wound healing problems, infection, seizures and swelling as the side effects of Gliadel Wafer. Specifically, Dr. Hamilton says, "The biggest problem that people have had with Gliadel have been early on there were some wound healing problems." He continues, "There were problems with infection. There were problems with wound leakage. There were problems with seizures. Most of those, I have to say, have been overcome." The video tape thus implies that many adverse events observed in clinical trials are no longer risks of using Gliadel Wafer. FDA is not aware of any data to support this claim. Furthermore, Dr. Hamilton mentions swelling as an effect that can be treated with

steroids, but fails to note that cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with Gliadel Wafer, including one case leading to brain herniation. The video tape thus fails to communicate significant risks associated with Gliadel, which are set forth in the PI, and misleadingly downplays the few adverse effects that are mentioned.

Additionally, Dr. Hamilton claims "Is there anything that says it's dangerous to take some drug with Gliadel? And the answer is no. You can start radiation after Gliadel. If your oncologist wanted to try you on another combination of chemotherapy, provided everything was going well and you had no complications from Gliadel, you can combine it." FDA is not aware of data to support this response and it contradicts the PI, which states, "Interactions of Gliadel with other drugs or radiotherapy have not been formally evaluated. In clinical trials, few patients have received systemic chemotherapy within 30 days of Gliadel or external beam radiation therapy. Chemotherapy was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery in patients undergoing re-operation for malignant glioma. External beam radiation therapy was initiated no sooner than three weeks after Gliadel implantation. Of the 36 patients who received Gliadel at initial surgery for newly diagnosed, malignant glioma followed by external beam radiation therapy, 3/15 (20%) in one study and 11/21 (52%) in the other study experienced new or worsened seizures. Patients were followed for a maximum of 24 months. The short and long-term toxicity profiles of Gliadel when given in conjunction with radiation or chemotherapy have not been fully explored."

Overstatement of Efficacy

In clinical studies, there were no statistically significant differences between the Gliadel Wafer and placebo groups with regard to improved patient-reported outcomes or time to neuroperformance deterioration. The following claim in the video tape is misleading because it suggests that Gliadel Wafer provides clinical benefits that have not been demonstrated by substantial evidence or substantial clinical experience:

> "There's a study that was just released, a frontline study of a randomized, placebo-controlled trial. …It made a remarkable improvement in survival. And the most important thing was, it helped sustain their neurologic function and their quality of life for a lot longer than the group that got the dummy wafer, the placebo wafer.... It improved not only survival, which is important, but it improved and sustained neurologic function for longer and, obviously, for patients that's an enormous issue, is the quality of life, not just how long they survived."

Furthermore, the claim "It made a remarkable improvement in survival" is misleading because it suggests a greater survival benefit than has been demonstrated by substantial evidence or substantial clinical experience. The referenced clinical trial involved 222 adults with recurrent malignant glioma who had failed initial surgery and radiation therapy. As stated in the PI, "Median survival increased by 33% from 24 weeks with placebo to 32 weeks with Gliadel treatment." As further stated in the PI, for patients with glioblastoma multiforme (GBM), "Median survival of GBM patients was increased by 41% from 20 weeks with placebo to 28

weeks with Gliadel treatment." These results are important for a hard-to-treat malignancy but viewers should be told that the “remarkable improvement” is in fact an 8 week improvement.

If Guilford has data to support the preceding claims, they should submit it to FDA.

Requested Action

Guilford should immediately cease the dissemination of this and other promotional materials for Gliadel Wafer that contain the same or similar claims. Guilford should submit a written response to DDMAC on or before October 10, 2003, describing its intent and plans to comply with the above. In its letter to DDMAC, Guilford should include the date on which this and other similarly violative materials were discontinued.

Guilford should direct its response to me by facsimile at (301) 594-6771, or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications (HFD-42), Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.
In all future correspondence regarding this matter, please refer to MACMIS ID #11459 in addition to the NDA number. DDMAC reminds Guilford that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Catherine A. Miller
Regulatory Review Officer
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/

Catherine Miller
9/29/03 01:41:19 PM