# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## 20-637/S-016

# Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-637\S-016

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

Dear Ms. Peltier:

Please refer to your supplemental new drug application dated April 6, 2001, received April 6, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gliadel Wafer (polifeprosan 20 with carmustine implant).

We also acknowledge receipt of your submissions dated April 25, May 25, June 1, 18, July 9, 12, 27, August 2, 9, 13, 15, 16, 27, September 4, 25, October 25, November 1, 20, 29, December 3, 4, 21, 2001, and January 18, 2002.

This supplemental new drug application proposes to expand the indication to include patients with malignant glioma undergoing primary and/or recurrent surgical resection.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Trial T-301, submitted as the primary evidence of efficacy, was a single, multi-center, randomized, placebo-controlled trial whose primary endpoint failed to reach statistical significance by the protocol-specified log rank test. The analysis of survival, which was the primary endpoint, showed no significant difference between study arms (log rank $p = 0.08$). The survival analysis you submitted ($p = 0.03$) was stratified by only one of four pre-specified covariates of interest (age, country, tumor type, and Karnofsky Performance Status). Analyses stratified by the other three factors or adjusted by all four factors showed no statistically significant difference.

To assess the impact of known prognostic factors on overall survival, a multivariate Cox model that adjusted for age, KPS and histology was used. The p value for the treatment effect increased to 0.16 in this analysis. We noted that there was a significant imbalance of gliomas with favorable histology, e.g., anaplastic oligoastrocytoma, which seems largely responsible for the borderline ($p = 0.08$) result of the overall analysis. When only patients with glioblastoma

multiforme are considered (that, after all was the only group showing an effect in your previous study #8802), the analysis reveals little suggestion of benefit for Gliadel ($p = 0.20$).

Your analyses of secondary endpoints that indicate a significant improvement in time to deterioration in Karnofsky Performance Status and time to deterioration in neurocognitive function were flawed because they included deaths as events. When deaths were censored, there was no consistent, statistically significant benefit for Gliadel.

For the reasons stated above, we have concluded that a beneficial effect of Gliadel on survival, overall function and neurological function in patients with newly diagnosed malignant glioma has not been adequately demonstrated.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the supplemental application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 594-5775.

Sincerely,

/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Richard Pazdur
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