

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21041

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21,041

Submission Dates: October 5, 15, 1998, February 5, 1999
Drug Name: Depocyt (Cytarabine Liposome Injection)
Dose and Formulation: 50 mg, 10 mg/mL, 5 mL Vial for Intrathecal Administration
Sponsor: Depotech Corporation
 San Diego, CA 92121
Reviewer: N.A.M. Atiqur Rahman, Ph. D.
Type of Submission: New Drug Application, 3P

BACKGROUND

This review focuses on the following issues:

- responses to the FDA comments that were provided to the sponsor in the review of the NDA
- Clinical Pharmacology and the Precautions sections of the package insert,
- in-vitro release specifications for Depocyt, and
- Phase IV pharmacokinetic (PK) protocol submitted to fulfill the requirement for the accelerated approval of the submitted NDA.

The NDA, 21,041 seeks approval of Depocyt for the intrathecal treatment of lymphomatous meningitis. The NDA was submitted to the Agency on April 28, 1997 seeking approval for the treatment of neoplastic meningitis of patients with solid tumors, lymphoma, or leukemia. The Clinical Pharmacology and Biopharmaceutics data was submitted in that NDA and reviewed by the Agency. The NDA was not approved; however, the Clinical Pharmacology and Biopharmaceutics comments were sent to the sponsor. In the resubmission (NDA 21,041), the sponsor provided no new pharmacokinetic data and responded to the comments that were provided to the sponsor in the review of the NDA.

I. Responses to FDA Recommendations and Comments

Item 1a. The sponsor's response is inadequate and unacceptable. The pharmacokinetics of Depocyt in the targeted population at the targeted dose using the to be marketed formulation has not been determined in NDA submission. The Phase IV commitment by the sponsor should address this issue.

Item 1b. The sponsor's response is acceptable.

Item 2a. In the NDA the sponsor provided in vitro release data up to four days. In the current submission, the sponsor has presented data from 6 lots up to 16 days in section 4 of NDA 21,041; submission dated October 15, 1998. The sponsor should provide 16 day profiles of the

clinical batches and at least one lot of the to be marketed batch for setting up an adequate in vitro release specification for the product.

Item 2b. The sponsor's response is acceptable.

Item 2c. The sponsor's response is unacceptable. See Item 2a. In the interim, the Agency proposed specification should be followed.

Responses to FDA General Comments

Item 2. The sponsor's response is unacceptable. However, the sponsor is not required to establish a link between the older process and the newer process since the pharmacokinetic data generated in the Phase 1 trial will only be considered supportive to the data that will be obtained in the Phase IV commitment.

Item 3. The sponsor's response is acceptable.

Item 4. The sponsor's response is unacceptable. Establishing optimal dose, frequency and duration of therapy for any disease condition are important for proper use of a drug. The clinical pharmacology information provided in the NDA is insufficient to establish optimal therapeutic regimen for Depocyt.

Item 5a. The sponsor's response is unacceptable. The Agency agrees that the study was not designed to establish bioequivalence on a statistical basis. However, a comparison of the pharmacokinetic profiles of cytarabine obtained with the drug products produced by the earlier and the improved processes is inappropriate due to a smaller sample size in the trials.

Item 5b. The sponsor's response is acceptable.

Item 5c. The sponsor's response is unacceptable. However, establishing bioequivalence between 1x and 10x DTC 101 lots are not required at this time.

Item 6. The sponsor's response is unacceptable.

Item 7. The sponsor's response is acceptable.

Item 8. The sponsor's response is acceptable.

Item 9: See item 2c.

II. Labeling

Comments:

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secret and/or

confidential

commercial

information

RECOMMENDATION:

The NDA 21,041 refers to the NDA for the Clinical Pharmacology and Biopharmaceutics information. The NDA 21,041 provides no data related to human pharmacokinetics. The Phase IV commitment should fulfill the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The Phase IV pharmacokinetic study protocol should be submitted to the Agency for review.

Please forward the comments to the sponsor.

FT ISI 3/19/99
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ISI 3/26/99
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cc: NDA 21,041 original
HFD-150 Division file
HFD-150 AStaten, GWilliams, Shirschfeld, LZhou, NChidambaram
HFD-205 FOI
HFD-850 LLesko
HFD-860 MMehta, ARahman
CDR BMurphy