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RESEARCH**

*APPLICATION NUMBER:*  
**21-763**

**APPROVABLE LETTER**



NDA 21-763

Biovail Technologies, Ltd.  
Attention: Jacqueline Little, M.Sc.  
Director, Regulatory Liason  
700 Route 202-206 North  
Bridgewater, NJ 08807

Dear Ms. Little:

Please refer to your new drug application (NDA) dated , received April 14, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Citalopram Hydrobromide Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated:

August 13, 2004	November 22, 2004	January 17, 2005
August 23, 2004	December 13, 2004	January 21, 2005
October 4, 2004	December 14, 2004	January 25, 2005
October 11, 2004	December 21, 2004	February 1, 2005

We completed our review of these applications, as amended, and they are approvable. Before this application may be approved, however, it will be necessary for you to address the following:

**Office of Clinical Pharmacology and Biopharmaceutics:**

- Based on the dissolution profiles of the biobatches, we accept the choice of the dissolution medium but believe that the method should be modified (especially the agitation speed) and the dissolution specifications need to be tightened. Following are the interim dissolution method and specifications recommended by the Agency:

Method: USP apparatus 2 (Paddle)

Speed: 100 rpm

Medium: 900 ml of pH 6.5 phosphate buffer for 40 mg ODT; 500 ml of pH 6.5 phosphate buffer for 10 mg and 20 mg ODT

Specification: Q = [redacted] in 30 minutes

- A Phase IV commitment was agreed upon during the teleconference of January 28, 2005, in which you agreed to:
  - Optimize the dissolution method and specifications using a lower agitation speed ([redacted] rpm with paddle) and a different dissolution medium if needed.

- o Generate data on biobatches and the next 3 production batches for all 3 strengths using the more optimized dissolution method. This data should be submitted to the Agency within 1 year from the date of approval for selecting a final dissolution specification for this product.

**Chemistry:**

- 1) DMF  $\eta$  [redacted] for citalopram hydrobromide has been found inadequate. The DMF will need to be found adequate in support of your NDA.
- 2) Update the release specifications for drug substance, citalopram hydrobromide, to include a test for specific [redacted] an identification test for [redacted] and a test for Melting Point (according to DMF holder's revised specifications).
- 3) Describe how the particle size distribution of citalopram hydrobromide is controlled batch to batch, since it is [redacted]
- 4) Describe the chromatographic parameters of the GC method used in the detection of the [redacted] (drug substance).
- 5) Provide actual values for Individual Impurity and Heavy Metal tests in the drug substance batch analysis.
- 6) [redacted]
- 7) Provide the equipment (class and sub-class) used in the CEFORM™ operation, a narrative description of the CEFORM™ technological process and batch records of the [redacted] (e.g., one batch of each strength manufactured at Dorado, PR site).
- 8) [redacted]
- 9) Provide all in-process controls and tests associated with the manufacture and packaging of Citalopram ODTs (including hardness and friability). Please include any updates in the citalopram [redacted] specifications.
- 10) Please provide a detailed sampling procedure for the drug product testing. The sampling plan should include details on the number of samples selected per batch and the location of the sample selected (e.g., beginning, middle, end).
- 11) According to 21 CFR 206 (Imprinting of solid oral dosage drug products for human use), a unique identification for the 10, 20 and 40 mg Citalopram ODTs should be clearly marked or imprinted on the tablets, or exemption request should be provided [21CFR 206.7 (b) (1)(ii)].
- 12) Provide a specification limit for moisture content (release and stability) for drug product. Include updated drug product specifications.
- 13) Since all packaging operations will be performed at the Dorado, PR facility (as per changes reported in the Amendment 10/04/04), it suggests the transportation of the Citalopram ODTs (packaged [redacted] at Dublin, Ireland site) to the Dorado, PR site. Provide stability data demonstrating that tablets manufactured at Dublin, Ireland and packaged at Dorado, PR are comparable to tablets manufactured and packaged at Dorado, PR. Stability data should include physical testing results (e.g., friability), which could evaluate any effect bulk storage/shipment has on commercial product and its storage (expiry).
- 14) In regards to the specificity of the HPLC method for assay and impurities, provide the chromatograms of the citalopram HBr spiked with quantitative amount of impurities,

- showing their resolution in the chromatogram of the same scale. Provide a description of \_\_\_\_\_, and "placebo" used in the validation of the HPLC method.
- 15) Based on the data presented in the submission, citalopram sample solutions (Identification I, Assay and Impurity Content test) were stable for 1 day at room temperature and not for \_\_\_\_\_ days as you stated. As a result, the test method will need to be corrected (i.e., sample solutions should be made daily) or data submitted to support the \_\_\_\_\_ days.
  - 16) Provide typical chromatograms with UV detection spectra over the range of \_\_\_\_\_ of the sample and standard citalopram solutions analyzed using a PDA detector (Drug Product Regulatory Specifications and Methods section).
  - 17) The sample solutions for Dissolution Method Validation were stable for \_\_\_\_\_ days and not for \_\_\_\_\_ days as you stated in the submission. As a result, the test method will need to be corrected (i.e., sample solutions should be kept for only \_\_\_\_\_ days) or data submitted to support \_\_\_\_\_ days.
  - 18) Provide actual disintegration values for all drug product test batches (release and stability data) submitted in the NDA.
  - 19) Explain the difference in the dissolution behavior between batch # PR-04-064R from that of the Biovail Dublin batch (lot #0307017) and the Biovail Dorado batch (lot # PR-04-044R) of the same 20 mg strength. Provide information on any manufacturing or formulation differences between these batches.
  - 20) Provide dissolution data at 30 and 60 minutes time points for drug product batches (all three dosage strengths) of the proposed marketed formulation manufactured at both sites, Dublin, Ireland and Dorado, PR (CoAs with detailed dissolution data are acceptable).
  - 21) Provide information on the holding time and stability data for the bulk ODTs at both manufacturing facilities, Dublin, Ireland and Dorado, PR.
  - 22) Submit the data from your Photostability study indicating whether the blister packaging protects the drug product against an increase in the level of the impurity, \_\_\_\_\_ upon exposure to UV and fluorescent light (provide control data). Include the statement "Protect from light" in the How Supplied section of the Package Insert.
  - 23) Please provide the container and carton labels for 10, 20 and 40 mg Citalopram ODTs.

The labeling should be identical in content to the enclosed labeling text for the package insert and text for the patient package insert.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

#### **Pediatric Research Equity Act (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Russell Katz

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