DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-323

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Mr. Friedman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) Tablets.

We acknowledge receipt of your submission dated August 2, 2004, requesting Agency feedback on your pediatric study proposal.

We have reviewed the referenced material and have the following comments and recommendations. For clarity, we have repeated your questions with our response immediately following the question.

1. Would a positive study using the "withdrawal design" (Study A) along with the positive results from the previous citalopram study (Study CIT-MD-18) and the supportive results from the previous escitalopram study (Study SCT-MD-15) be adequate to support a claim for escitalopram use in *acute treatment phase* in addition to maintenance treatment phase in pediatric patients aged 12 to 17 years?

   Differently designed studies of an overlapping age population need to be similar enough to provide some sense of replication. In this case, an additional relapse prevention designed study in adolescents alone would not suffice to grant a claim for adolescent major depressive disorder (MDD). This is even assuming that Forest would use the CDRS and not the MADRS as planned. The study designs and age groups are different enough that we do not feel that the results had been replicated. We do not concur with your position that the *post hoc* analysis of the failed trial is supportive of efficacy from a regulatory perspective.

2. Would a positive study with escitalopram using a conventional acute treatment design (Study B) along with the previous positive study with citalopram (Study CIT-MD-18) be adequate to support an indication for acute treatment in pediatric patients aged 12 - 17 years?

   We believe that one additional positive acute treatment study of adolescents in addition to Study CIT-MD-18 would support a claim for the acute treatment of adolescents with MDD. In this case, the study designs would be similar enough to provide a sense of replication.

Again, we do not concur with your position that the *post hoc* analysis of the failed trial is supportive of efficacy from a regulatory perspective.

3. Can the MADRS or CGI-S be used as the primary efficacy parameter instead of CDRS-R?

   The CGI-S is inappropriate as a primary variable in a study of MDD, though it could be used as a co-primary with the CDRS or as a key secondary variable. Though the MADRS might, at some point, prove to be appropriate for adolescents, the CDRS is specifically designed and validated for children and your assertion that the MADRS is appropriate seems speculative at this point. In a MEDLINE literature search, we were only able to find one controlled study performed in France that used the MADRS in the adolescent population. This was a comparative study of paroxetine and clomipramine that failed to show any difference in efficacy between the two drugs[1]. Since there was no placebo group, it also was not able to demonstrate whether there was any drug effect. We are therefore not prepared to endorse the MADRS as an acceptable rating scale at this point from a regulatory perspective.

If you have any questions, call Paul David, Senior Regulatory Health Project Manager, at (301) 594-5530.

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

[1] Braconnier A, Le Coent R, Cohen D; DEROXADO Study Group Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. J Am Acad Child Adolesc Psychiatry. 2003 Jan;42(1):22-9..Department of Adolescent Psychiatry, Centre Philippe Paumelle, Paris, France.

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/s/

Russell Katz

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