

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-822 SE5-016

Sponsor: Forest Labs

Drug: Celexa. (citalopram hydrochloride)

Material Submitted: Pediatric Supplement SE5-016

Date Submitted: 4/18/02

Date Received: 4/19/02

Medical Reviewer: Earl D. Hearst, MD

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Only one of two clinical studies is positive and this supplement is not approvable.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In our 7/12/02 memo we asked to the sponsor to submit open-label 24 week safety data from these studies at a later date.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two pharmacokinetic (CIT-PK-07 and CIT-PK-13) and two clinical studies (94 404 and CIT-MD-18) were submitted.

. CIT -PK-07 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. CIT -PK-13 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. 94 404 "A Double-blind Study Comparing Citalopram Tablets and Placebo in the Treatment of Major Depression in Adolescents."

. CIT-MD-18 "A Randomized Double-Blind, Placebo-controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents."

B. Efficacy

Only one of the two clinical studies can be considered positive.

. CIT-MD-18

On the primary efficacy parameter, the change from baseline in CDRS-R at Week 8, citalopram produced significantly greater improvement than placebo.

Change from Baseline to Week 8 in CDRS-R [Mean \pm SEM]			
	Placebo (N=85)	Citalopram (N=89)	p-value
Mean \pm SEM	-16.5 \pm 1.6	-21.7 \pm 1.6	0.038

The citalopram group exhibited significantly greater improvement than the placebo group beginning at Week 1 and at all subsequent clinic visits. Analysis of the response rate on the CDRS-R also revealed a significantly higher percentage of responders (CDRS-R \leq 28 at study endpoint) in the citalopram group (36.0%) as compared to the placebo group (23.5%) (p=0.041).

. 94 404

In this 12-week study, a therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be found. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram.

C. Safety

There are no significant safety issues in this population. See studies below.

CIT-MD-18

No deaths occurred during the conduct of the study. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient.

94 404

No deaths occurred during the study.

Withdrawals due to AEs occurred for 9% of the patients and were similarly distributed among treatment groups.

SAEs were reported by 16 patients in the placebo group and by 18 patients in the citalopram group. The majority of the patients with SAEs reported hospitalizations due to psychiatric disorders (9 patients in the placebo group and 14 patients in the citalopram group). In the placebo group, the other SAEs were surgical interventions (3 patients), epileptic fit, head trauma, medication error, and hospitalization for social reasons. In the citalopram group, the other SAEs were dyspnea, non-suicidal overdose, hospitalization for social reasons, and abortion.

CIT -PK-07

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event.

There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

CIT -PK-13

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event. There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

D. Dosing

CIT-MD-18

The clinical trial was conducted as a randomized, double-blind, placebo-controlled, multicenter, parallel-group, 2-arm, flexible dose study comparing citalopram (20-40 mg/day) with placebo in pediatric outpatients diagnosed with MDD. The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents.

94404

This was a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose study. At screening, patients were randomly assigned to 12 weeks of double-blind treatment with either citalopram 10mg daily or placebo. Based on the investigator's clinical evaluation, there was a possibility of a 10mg dose increase for patients in the citalopram group at the end of Week 1 (to a maximum of 20mg), Week 2 (to a maximum of 30mg), Week 5 (to a maximum of 40mg), or Week 9 (to a maximum of 40mg). The mean citalopram serum concentrations at Week 12 were 130, 217, and 288nmol / L after treatment with 20, 30, or 40mg, respectively.

E. Special Populations

94404

No consistent pattern in serum levels in males as compared to females was observed.

CIT-MD-18

The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents. However, the correlation analyses revealed no significant correlation between age and citalopram concentration ($r=-0.059$; $p=0.650$) or escitalopram concentration ($r=0.048$; $p=0.714$). Body weight also appeared to be uncorrelated with either citalopram concentration ($r=-0.218$; $p=0.089$) or escitalopram concentration ($r=-0.119$; $p=0.357$). Improvement on the CDRS-R also showed no significant relationship to plasma levels of either citalopram ($r=0.123$; $p=0.341$) or its active enantiomer escitalopram ($r=0.104$; $p=0.422$).

F. Exclusivity

Exclusivity has been granted based on the completion of these studies.