CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Celexa ® (Citalopram)
NDA: 20-822 SE5-016
21-046 SE5-002
FORMULATION: Tablets/Solution
APPLICANT: Forest Labs.

PRIMARY REVIEWER: Vanitha J. Sekar, PhD

TYPE: Pediatric efficacy suppl (7-17 years)
STRENGTH: 10, 20, 40 mg, Solution 2 mg/ml
SUBMISSION DATE: 4-18-02

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Overall Summary of Findings: This submission (response to pediatric written request) contains results from 3 in-vivo studies: 1) Single dose (20 mg) pharmacokinetic study in 12 healthy children aged 7-11 years and in 12 adults, 2) multiple dose (40 mg/day maintenance dose) pharmacokinetic study in 13 pediatric depressed patients aged 10-17 years and in 12 adults, 3) Efficacy trial in pediatric depressed patients aged 7-17 years in which steady-state trough concentrations were measured (n=45 children 7-11 years and n=44 children aged 12-17 years). Only one of the 2 clinical efficacy studies demonstrated efficacy of Celexa in the pediatric population – the second study is a failed study. As a result, the Clinical Division stated at the filing meeting that Celexa will not be approved for use in the pediatric population at this time and no labeling recommendations related to the pediatric population will be made. This Clinical Pharmacology/Biopharmaceutics review will therefore focus only on results from the traditional pharmacokinetic studies and the descriptive statistics for the pharmacokinetic information obtained in the clinical trial to evaluate whether the applicant has adequately evaluated the pharmacokinetics of Celexa in the pediatric population and if the pharmacokinetics of Celexa are similar in the pediatric population and in adults.

The sponsor has conducted 2 traditional pharmacokinetic studies – one single dose study (20 mg citalopram oral solution) in healthy children (aged 7-11 years) and adults, and a second multiple dose study in depressed adolescents (aged 10-17 years) and in depressed adults given 20 mg citalopram once daily with forced titration to 40 mg once daily for a total of four weeks. In the single dose study, higher C_{max} (114%), larger $AUC_{0-\infty}$ (33%), and smaller CL/F (28%) for citalopram were observed in children compared to adults. However, in the multiple dose study pharmacokinetic parameters of citalopram after a single dose of 20 mg citalopram and after multiple doses of 40 mg once daily were similar in depressed adolescents and adults. In addition, in efficacy trial CIT-MD-18 (in depressed children and adolescents aged 7-17 years), the sponsor has collected a blood sample (between 8-14 hours post dose) for the measurement of citalopram steady-state concentrations in plasma. In this study, the steady-state concentrations of citalopram were approximately 13% higher in the children as compared to the adolescents. Correlation analyses revealed no significant correlation between age and citalopram concentration (r=0.059, p=0.650) as well as body weight and citalopram concentration (r=-0.218; p=0.089).

These results suggest that the pharmacokinetics of Celexa are similar in adolescents and in adults. However for younger children (7-11 years of age), the single dose pharmacokinetic data suggest a higher exposure in the pediatric population compared to adults. Data from the sparse sampling pharmacokinetic study (in the efficacy trial) need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adults/adolescents.

Recommendation: The pharmacokinetic studies provided in this pediatric supplement for Celexa submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of citalopram in pediatric patients between the ages of 7 and 17 years, inclusive. This submission is acceptable from OCPB perspective. Data from the sparse sampling pharmacokinetic study need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adolescents/adults.

Comment: At the time when data from the sparse sampling pharmacokinetic study are analyzed further, the sponsor will be requested to submit the exact sampling time relative to dosing for all of the sparse sampling data.

Introduction and Background: Celexa™ (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Celexa is available as 10 mg, 20 mg and 40 mg film coated tablets and also as an oral solution (2 mg/ml).

Celexa (citalopram HBr), in adults, is labeled to be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of not less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that citalopram is a selective serotonin reuptake inhibitor with minimal effects on norepinephrine and dopamine neuronal reuptake. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer .

The single and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram, demethylcitalopram, and didemethylcitalopram to human plasma proteins is about 80%. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent. Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours.

Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram citalopram-N-oxide and a deaminated propionic acid. In humans, citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, demethylcitalopram and didemethylcitalopram in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. In vitro studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram is expected to be 2.5 times the plasma concentrations observed following a single dose. Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and demethylcitalopram was about 10% and 5%, respectively. The systemic clearance of citalopram is 330 ml/min, with approximately 20% of that due to renal clearance.

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2El, but did suggest that it is a weak inhibitor of CYP-IA2, -2D6, and -2C19. However, in vivo data to address this question are limited. Coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple dose administration of Celexa.

Clinical Pharmacology

1 a. Has the sponsor adequately evaluated the pharmacokinetics of Celexa in the pediatric population?
1. b. Are the pharmacokinetics of Celexa similar in the pediatric population and in adults?

In a single dose pharmacokinetic study (PK-13) of 20 mg citalopram oral solution in healthy children (aged 7-11 years) and adults, the rate of absorption of citalopram was faster and the extent of absorption was larger in children compared to adults. A shorter t_{max} (24%), higher C_{max} (114%), larger $AUC_{0-\infty}$ (33%), and smaller CL/F (28%) for citalopram were observed in children compared to adults. Similar conclusions were obtained when adjustments were made for differences in body weights between the subject populations. No gender effects on pharmacokinetic parameters (except citalopram T_{max}) were found for citalopram in this study. T_{max} (11%) for citalopram was shorter in females than in males.

In a multiple dose pharmacokinetic study (PK-07) in children (aged 10-17 years) and in adults given 20 mg citalopram once daily with forced titration to 40 mg once daily for a total of four weeks, pharmacokinetic parameters of citalopram after a single dose of 20 mg citalopram and after multiple doses of 40 mg once daily were similar in depressed adolescents and adults. Comparison of pharmacokinetic parameters between male and female patients revealed no significant gender effects for citalopram.

Comparison of the pharmacokinetics of citalopram and demethylcitalopram following a single 20 mg dose across the above 2 studies (PK-13 and PK-07) suggests that younger children (aged 7-11 years) have higher AUC (approximately 30%) and Cmax (60-100%) than adolescents and adults following a single 20 mg dose of citalopram.

However, in efficacy trial CIT-MD-18 (in depressed children and adolescents aged 7-17 years), the sponsor has collected a blood sample for the measurement of citalopram steady-state concentrations in plasma. Wherever possible, the sample was collected between 8-14 hours after the last dose of study medication was taken. In this study, the steady-state concentrations of citalopram were approximately 13% higher in the children as compared to the adolescents. Correlation analyses revealed no significant correlation between age and citalopram concentration ($r=0.059$, $p=0.650$). Body weight also appeared to be uncorrelated with either citalopram concentration ($r=-0.218$; $p=0.089$). Tables and figures supporting these results are attached in the appendix. There is a variability in sampling times, no pharmacokinetic modeling was performed on this data, and (13%) increased concentrations were observed in children compared to adolescents. Therefore, data from the sparse sampling pharmacokinetic study need to analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adolescents/adults.

Conclusions: These results suggest that the pharmacokinetics of Celexa are similar in adolescents and in adults. However for younger children (7-11 years of age), the single dose pharmacokinetic data suggest a higher exposure in the pediatric population compared to adults. Data from the sparse sampling pharmacokinetic study (in the efficacy trial) need to be analyzed further to be able to conclude similarity or differences in pharmacokinetics between younger children (7-11 years) and adults.

Labeling comments: Since Celexa will not be approved for use in the pediatric population at this time, no labeling recommendations will be made.

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