that since the dose of OXC will be titrated in patients receiving CBZ or PHT if their seizures are not controlled, the lower MHD exposure following coadministration with CBZ/PHT is probably not clinically significant. However, the observed decreases in MHD AUC of 40% and 30% following coadministration with CBZ and PHT, respectively, must be clearly stated in the label to alert clinicians of the decrease in MHD exposure when OXC is administered with these two drugs.

Effects of phenobarbitone (PB) and sodium valproate (VPA) on the Pharmacokinetics of Oxcarbazepine: The study was designed to assess the pharmacokinetic profile of MHD after a single, oral dose of 600 mg in epileptic patients chronically treated with either VPA or PB monotherapy, in comparison with the pharmacokinetic profile of MHD after the same single dose in drug-free healthy subjects. The doses of PB ranged from 100-150 mg/day and the doses for VPA ranged from 1000-2000 mg/day. Patients on PB have approximately 30% lower plasma concentrations than healthy, drug-free subjects, as determined from the differences in AUC of MHD between the 2 groups. This suggests that MHD metabolism is induced by PB, resulting in lower concentrations of the former. MHD metabolism is therefore, moderately affected by PB coadministration. The pharmacokinetics of MHD between healthy, drug-free subjects and patients on VPA were not significantly different. These results suggest that VPA does not inhibit the enzymes involved in the glucuronidation of MHD.

Effects of Viloxazine on the Pharmacokinetics of Oxcarbazepine: The study was designed as a double blind, placebo-controlled, 2-treatment, crossover study in epileptic patients to assess the effects of repeated doses of viloxazine 100 mg bid for 10 days) on the pharmacokinetics of OXC (individualized regimen). All patients were on OXC monotherapy for at least one month preceding the trial. Plasma steady-state concentrations of unchanged OXC were not influenced by viloxazine coadministration. The concentrations of the major and pharmacologically active metabolite, MHD were approximately 10% higher after coadministration with viloxazine compared to those following OXC alone. Plasma concentrations of the pharmacologically inactive metabolite, DHD, decreased by approximately 31% following coadministration of OXC. These differences are small and probably not clinically significant .

Effects of Verapamil on the Pharmacokinetics of Oxcarbazepine: The study was designed as a non randomized, open label study in healthy males to assess the effects of a single (120 mg) and repeated doses of verapamil (120 mg bid for 7 days) on the steady-state pharmacokinetics of OXC (titration of OXC to a daily dose of 450 mg bid). The exposure to the main and pharmacologically active metabolite, MHD, following coadministration of OXC and of verapamil (single and multiple doses), was approximately 20% lower than the exposure following OXC alone. Lower exposure and Cmax (of approximately 50%, in each case) were obtained for the minor and inactive metabolite, DHD, following coadministration of OXC and verapamil (multiple doses). However, these differences, probably due to an inhibition of the oxidation of MHD, are probably not clinically relevant.

Effects of steady state erythromycin on the pharmacokinetics of OXC: The study was designed as an open label, randomized, crossover study in healthy volunteers to assess the effects of repeated doses of erythromycin (500 mg bid for 7 days) on the pharmacokinetics of a single dose OXC (600 mg). Results from the analysis showed that were no significant differences in MHD exposure and Cmax following coadmiistration with OXC. The bioavailability of the active metabolite, MHD is unchanged following coadministration with erythromycin.

Effects of steady state cimetidine on the pharmacokinetics of OXC: The study was designed as an open label, randomized, crossover study in healthy volunteers to assess the effects of repeated doses of cimetidine (400 mg bid for 7 days) on the pharmacokinetics of OXC (600 mg). Results from the analysis showed that were no significant differences in MHD exposure and Cmax following coadmiistration with OXC. The bioavailability of the active metabolite, MHD is unchanged following coadministration with cimetidine

Effects of steady state dextropropoxyphene on the pharmacokinetics of OXC: The study was designed as an open label, non randomized study in epileptic patients to assess the effects of repeated doses of dextropropoxyphene (65 mg tid for 7 days) on the steady-state pharmacokinetics of OXC (individualized regimen of 750-2700 mg bid). The pharmacokinetic parameters of the main and pharmacologically active metabolite, MHD, following OXC alone and those following coadministration of OXC and dextropropoxyphene were not significantly different. Lower exposure and Cmax were obtained for the minor and inactive metabolite, DHD, following coadministration oi OXC and dextropropoxyphene. However, these differences, probably due to an inhibition of the oxidation of MHD, are probably not clinically relevant. No dosage adjustment for either drug is recommended.

EFFECTS OF OXC ON COADMINISTERED DRUGS

Effect of OXC on the Pharmacokinetics of Concomitantly Administered Antiepileptic Drugs (CBZ, VPA and PHT): The applicant conducted a study to investigate the pharmacokinetic interactions following addition of OXC, as a single dose (600 mg), and after 3 weeks of continuos administration (300 mg tid) to epileptic patients currently treated with multiple (individualized) doses of CBZ, VPA or PHT monotherapy.

Antiepileptic drug	Group	AUC0-12 (μg.h/ml) as Mean (Range)	Geometric mean ratio and 90% CI
CBZ	CBZ with OXC	101 (	
	CBZ with Placebo	94.0 (	1.08 (
CBZ-10, 11-E (Active metabolite of CBZ)	CBZ with OXC	16.6 (	
	CBZ with Placebo	12.8 (	1.30 (
VPA	VPA with OXC	1090	
	VPA with Placebo	1190	0.92 (
PHT	PHT with OXC	333 (	
	PHT with Placebo	305 (	1.09 (

The differences in the steady state exposure for CBZ, VPA and PHT groups in the presence of OXC and placebo were small and not statistically significant. These differences were an 8% increase, 8% decrease and 9% increase for steady state CBZ, VPA or PHT exposure, respectively. These differences in CBZ, VPA and PHT exposures are probably not clinically significant. However, a statistically significant 30% increase in steady state AUC0-12 for the metabolite of CBZ (CBZ 10, 11-E) was observed after concomitant administration of CBZ and OXC compared to that following CBZ and placebo. A dosage adjustment has not been recommended since the dose of OXC will be titrated in patients receiving CBZ if their seizures are not controlled. However, the observed increase in steady state exposure for the metabolite of CBZ following coadministration with OXC must be stated in the label

Effects of OXC on the steady state pharmacokinetics of the oral contraceptive, Triquilar: An open label, non randomized within-patient study was conducted to assess the effects of single (300 mg) and multiple dose (titrated to 300 mg tid) OXC administration on the steady state pharmacokinetics of ethinyl estradiol (EE) and levonorgestrel (LNG). Compared to the treatment without OXC, AUC values for EE and LNG were significantly lower during treatment with OXC (48% and 32%, respectively). However, the decrease in mean Cmax values was not statistically significant. Of the 10 volunteers, 4 had a greater than 50% decrease in EE AUC, 5 had a decrease in EE AUC of 13-35%, and 1 volunteer had an increase in EE AUC of 29%. For LNG, 2 volunteers had a greater than 50% decrease in AUC, 7 had a decrease in AUC of 18-43%, and 1 volunteer had an increase in AUC of 42%. The applicant postulates that the decrease in EE exposure may be due to a specific inducing effect of repeated doses of OXC on the major metabolic pathway (2-hydroxylation via P4503A) of EE. This is in agreement with results from previous in-vitro and in-vivo studies with OXC that showed that OXC has the capacity to induce enzymes from the CYP 3A4 sub family. Also, alterations in the extent of first pass metabolism, conjugation or protein binding may play a role in altering the pharmacokinetics of EE and LNG after coadministration with OXC. Female patients must therefore use alternate and additional forms of birth control when taking OXC.

The applicant conducted another study to assess the effects of multiple doses of OXC (1200 mg/day) on the steady state pharmacokinetics of two active ingredients of the oral contraceptive, Evanor-D, in healthy females. The active ingredients in the oral contraceptive were ethinyl estradiol (EE) and levonorgestrel (LNG). Progesterone trough concentrations were measured as a pharmacodynamic endpoint to evaluate the occurrence of ovulation. This study was conducted to confirm the findings in the earlier study using OXC and oral contraceptives, which showed that concentrations of EE and LNG were reduced significantly (48% and 32%, respectively) when coadministered with OXC. This study utilized higher doses of OXC as well as the oral contraceptive than the earlier study. Compared to the treatment with placebo, AUC values for EE and LNG were significantly lower during treatment with OXC (approximately 52% in each case). Mean Cmax values for EE and LNG were also decreased moderately during treatment with OXC when compared to placebo. The mean progesterone concentrations during the OXC treated and placebo phases of the study were 0.53 ± 0.32 and 0.55 ± 0.28 μmol/L, respectively. The similarity of progesterone trough concentrations suggests that the decrease in EE and LNG concentrations during OXC treatment did not result in a change in progesterone levels and hence trigger an ovulation. However, it was noted that two intermenstrual bleedings occurred during the trial during treatment with OXC (both in the same subject). Intermenstrual bleeding in this subject was interpreted clinically as a sign of contraceptive failure. This study also demonstrated that concomitant administration of OXC with oral contraceptives may not provide sufficient protection from conception. Female patients must therefore use alternate and additional forms of birth control when taking OXC.

Effects of single and repeated doses of OXC on the pharmacokinetics of felodipine: Felodipine is a calcium antagonist used in the treatment of hypertension, angina pectoris and heart failure. Felodipine is metabolized by the microsomal cytochrome P-450 enzyme; interactions with drugs that are metabolized by the same enzymes may be anticipated. OXC is largely metabolized by non-oxidative processes. However, results from previous in-vitro and in-vivo studies with OXC that showed that OXC has the capacity to induce enzymes from the CYP 3A4 sub family. The study was designed to investigate the possible influence of single (600 mg) and repeated doses of OXC (400 mg bid) on the steady state pharmacokinetics of felodipine (10 mg qd for 13 days) in healthy volunteers. The pharmacokinetics of felodipine and its pyridine metabolite following administration of felodipine alone were similar to those following coadministration with a single 600 mg dose of OXC. Following repeated administration of OXC (450 mg bid), the mean exposure and Cmax for felodipine were 28% and 34% lower, respectively, compared to that following felodipine alone. However, the plasma concentrations of felodipine were still in the recommended therapeutic range. Similar results were obtained for the pyridine metabolite of felodipine. No change in its pharmacokinetic parameters were observed after coadministration with a single dose of OXC. However, after coadministration with repeated doses of OXC, the mean exposure and Cmax were lowered by 37% and 35%, respectively. Since coadministration with OXC did not increase the exposure to the pyridine metabolite of felodipine, the metabolic processes involved in the oxidation of felodipine to the pyridine metabolite are probably not affected by OXC. The reduction in the felodipine exposure by 28% due to concomitant administration with OXC may be due to the influence of OXC on other metabolic pathways of felodipine. The bioavailability of felodipine and its metabolite is decreased following coadministration with OXC. However, since felodipine concentrations were still in the therapeutic range, no dosage changes for felodipine have been recommended.

Effect of single and repeated doses of OXC on the Pharmacodynamics of Warfarin: The objective of this study was to investigate the pharmacodynamic effect of Coumadin (sodium warfarin) under steady state conditions, before and after treatment with single (600 mg) and multiple doses (450 mg bid) of OXC. During warfarin titration phase, the warfarin dose was titrated to achieve a Quick Time (measure of prothrombin time) of 35-45%. During the warfarin maintenance phase, the warfarin dose was maintained at the level established during the titration phase. Because the Quick times were found not to be reaching the target range of 35-45% in most subjects during the planned warfarin titration phase, this period was extended to day 20.

Consequently, the warfarin dose was held constant for only one week before OXC treatment was started. the effects of chronic OXC treatment on warfarin pharmacodynamics were assessed by comparing the results from Quick times before and after coadministration with OXC. Statistical analysis using paired t-tests showed that the Quick times were not significantly different. This prothrombin time in healthy volunteers on steady-state warfarin therapy is not significantly altered by a single 600 mg oral dose of OXC or by repeated doses of 450 mg bid of OXC. These results suggest that OXC does not affect the pharmacodynamic effects of warfarin.

ADVERSE EXPERIENCES

Common adverse events regardless of relationship to trial drug were defined as those that occurred in at least 10% of OXC-treated patients. Adverse events that were most frequently reported included side effects for the nervous system, the digestive system, and the body as a whole. In descending order of frequency, the common adverse events were headache, dizziness, somnolence, nausea, vomiting, diplopia, viral infection, and fatigue. The adverse events experienced by OXC-treated healthy subjects in Clinical Pharmacology trials were consistent with those experienced by the OXC-treated epileptic patients.

COMMENTS TO APPLICANT

1. Please provide a rationale for the proposed dissolution medium and the proposed dissolution specifications. Review of the individual dissolution data indicates that a specification of ( ) would be appropriate for all 3 strengths of Trileptal.

2. Exposures in children (especially in children 2-6 years of age) were found to be lower than in adults at comparable doses. The recommended starting dose in these children may be lower than that required for seizure control. It is recommended that the applicant evaluate the pediatric population further in order to recommend an appropriate dosing regimen in this population.

LABELING COMMENTS

(~~Strikeout text~~ should be removed from the label. Double underlined text should be added to the label. ☛ indicates an explanation of what should be included/added to the label)

Pharmacokinetics
Absorption
After single dose administration of 600 mg Trileptal to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 (Standard deviation) μmol/L with a corresponding median t_{max} of 4.5 (range) hours.

Special Populations
Hepatic Impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD.

Renal Impairment
There is a linear correlation between creatinine clearance and the renal clearance of MHD. When Trileptal is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two fold increase in AUC.

osa

PRECAUTIONS

Drug Interactions

Antiepileptic drugs

- For Table 3A: **Summary of AED Interactions**: Please indicate clearly in the label whether the changes observed are changes in AUC or Cmin. Also please include in each case, a measure of variability, such as 90% confidence interval. The following format for the table (3A) is recommended.

Coadministered AED	Dose of AED	OXC Dose	N	Coadministered AED (% Change)		MHD (% Change)	
				AUC mean (90%CI)	Cmin mean (90%CI)	AUC mean (90%CI)	Cmin mean (90%CI)

Hormonal Contraceptives

- Please include in a measure of variability, such as a 90% confidence interval along with the mean change in AUC of the coadministered drug(s).

Calcium Antagonists

- Please include in a measure of variability, such as a 90% confidence interval along with the mean change in AUC of the coadministered drug(s). The following format for an additional table (3B: **Summary of interactions with other drugs**) is recommended.

Coadministered AED	Dose of Coadministered drug	OXC Dose	N	Coadministered Drug(% Change)		MHD (% Change)	
				AUC mean (90%CI)	Cmin mean (90%CI)	AUC mean (90%CI)	Cmin mean (90%CI)

1 page
REDACTED
DRAFT
LABELING

/S/

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drugs Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Concurrence: Chandra Sahajwalla, Ph.D.
Team Leader, Neuropharmacological Drugs Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics
cc: HFD-120 NDA 21014
/MO/N. Hershkowitz
/CSO/M. Malandrucco
/Biopharm/V.Sekar
/TL Biopharm/C. Sahajwalla
HFD-340 /Viswanathan
HFD-860 /DPE1
CDR Document Room

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-014	**REVIEWERS:** Vanitha J. Sekar, Ph.D. Vijaya K. Tammara, Ph. D.
DRUG: Oxcarbazepine (Trileptal™)	**FORMULATION(S):** 150, 300, 600 mg tablets
(RE)SUBMISSION DATE:11/16/99	**APPLICANT:** Novartis

BACKGROUND: *This resubmission contains the applicant's responses(s) to the comments sent by the Agency in the approvable letter.*

Response to Comment #2 re: drug interaction studies with diazepam and omeprazole (2C19 substrates):

The applicant has proposed to conduct an ***in-vitro*** drug interaction study to evaluate the potential interaction of diazepam and omeprazole with oxcarbazepine and MHD. This proposal is

acceptable. Based on the results from this in-vitro study, an in-vivo drug interaction study may or may not be required.

Pediatric Indication:

In addition to the above 2 Biopharm comments, the applicant has also responded to the Indication Section of the Label, with reference to the use of Trileptal in pediatric patients (as adjunctive as well as monotherapy). The applicant was sent a comment by the Division of Neuropharmacological Drug Products that Trileptal would only be indicated as adjunctive therapy in pediatric patients between the ages of 8-16 years, since sufficient safety and efficacy data was not available for monotherapy use or as adjunctive therapy in children aged less than 8 years. The applicant has responded to this comment; in addition to efficacy information, this response also contains pharmacokinetic analysis comparing MHD exposure in adults and in children aged 3-17 years (following adjunctive therapy).

The applicant has presented the following comparisons of pharmacokinetics of MHD between children and adults following adjunctive therapy with Trileptal:

Comparison of pediatric and adult pharmacokinetics of MHD for monotherapy

Age (yrs)	Weight (kg)	Significant Concomitant AEDs	Average Clearance [Cl/F] (L/hr/kg)	Analysis Method	Reference
3-5 (N=11)	16-26	None	[redacted]	Population PK model	Study 011
4-5 (N=4)	15-22	None	0.073	Non-compartmental	Study OT/F11
6-17 (N=96)	26 to 85	None	[redacted]	Population PK model	Study 011
9-15 (N=8)	26-74	None	0.061	Non-compartmental	Study OT/F11
8-63 (N=24) Children and Adults	26-103	None	0.043*	Population PK model	Study 025~
12-65 (N=104) Children and Adults	41-152	None	0.041*	Population PK model	Study 026~
Adult		None	0.046*	Population PK model	Study 011
Adults (N=20)		None	0.042*	Non-compartmental	Study 029

*Based on a typical adult weight of 70 kg.
~N=6 for age 8-16 yrs.
~N=7 for age 12-20 yrs.

Overall, from the above comparison of data particularly from pivotal clinical studies (study 011, study 025, and study 026), it can be concluded that the pharmacokinetics is similar between older children (age > 8 yrs) and adults. However, younger children (< age of 8 yrs) clear the drug faster than older children and adults [redacted]. Therefore, starting dose in children under the age of 8 yrs should be accordingly adjusted. A similar and recommendation was given in the original NDA review dated August 20, 1999.

LABELING COMMENTS:

1. The sponsor is requested to replace the following statement under Clinical Pharmacology, special populations, Pediatric use section:

[redacted]

With:

[redacted]

2. The sponsor's summary of AED interactions under Precautions, Drug Interactions, Antiepileptic Drugs section of the labeling should be replaced with:

Summary of AED interactions with Trileptal and Vice versa

Coadministered AED	Dose of AED mg	OXC Dose mg	N	Coadministered AED (% Change) AUCss mean (90%CI)	MHD (% Change) AUCss mean (90%CI)
Carbamazepine (CBZ)	400-2000	900	12	↑ 8 [redacted]	↓ 40 [redacted]
CBZ-epoxide				↑ 30 [redacted]	
Phenytoin	250-500	900		↑ 9 [redacted]	↓ 30 [redacted]
Valproic acid	400-2800	900		↓ 8 [redacted]	↓ 18 [redacted]
Phenobarbital	< 100	600	?	?	?

3. Adjunctive therapy in pediatrics (age 4 – 17 yrs): The pharmacokinetics of Trileptal is similar between older children (age > 8 yrs) and adults. However, in younger children (< age of 8 yrs) the clearance of Trileptal increased by abou[redacted] compared to older children and adults. Therefore, starting dose in children under the age of 8 yrs should be accordingly adjusted.

4. The sponsor is requested to adapt the following dissolution methodology and specifications for 150, 300 and 600-mg tablet strengths of Trileptal:

[redacted]

Vijay K. Tammara, Ph. D.
Team Leader, Division of Neuropharmacological Drug Products
Division of Pharmaceutical Evaluation I

RD/FT Initialed by C. Sahajwalla, Ph. D. (Deputy Director) ----------

CC: NDA 21,014, HFD-120, HFD-860 (Tammara, Sekar, Sahajwalla, Mehta), CDR (for Drug Files).

AUG 20 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-014	**REVIEWER:** Vanitha J. Sekar, Ph.D.
DRUG: Oxcarbazepine (Trileptal™)	**TEAM LEADER:** Chandra Sahajwalla, Ph.D.
FORMULATION(S): 150, 300, 600 mg tablets	**SUBMISSION DATE:** September 25, 1998
APPLICANT: Novartis	

TABLE OF CONTENTS

SYNOPSIS

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently registered in 47 countries. OXC is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active. The applicant is seeking approval of oxcarbazepine (Trileptal™) tablets in the USA for oral administration.

Film-coated tablets (150, 300 and 600 mg strengths) were developed as the final dosage from of OXC to be marketed in the USA. The pivotal bioequivalence study was conducted using the highest strength (600 mg) of the final market image formulation. Following single and multiple doses, under fed conditions, the 600 mg to-be–marketed tablet was found to be bioequivalent to the pivotal trial formulation. Food did not have an effect on the bioavailability of the final market formulation (600 mg), whereas the non-US current market formulation was shown to have a significant food effect. The applicant's request for a waiver of a bioequivalence study for the two lower strengths of Trileptal (150 and 300 mg) is based upon comparable multi-media dissolution profiles, compositional proportionality of the 3 strengths of OXC tablets and high permeability (F>95%) of the drug, which is acceptable.

Trileptal is recommended for use either as monotherapy or in combination with other antiepileptic drugs. In mono- and adjunctive therapy, the applicant recommends treatment with Trileptal to be initiated at a dose of 600 mg/day (8-10 mg/kg/day) given in two divided doses. The dose may be increased depending on the clinical response of the patient. Doses of up to 4200 mg/day have be administered in a limited number of patients in order to achieve a maximum therapeutic effect. Drug plasma level monitoring is not a recommendation for Trileptal.

Mass balance studies showed that most of the dose (over 94%) was renally excreted as - monohydroxy (MHD) and less than 5% was excreted in the feces, suggesting that OXC is almost completely absorbed from the gastrointestinal tract. Very low (approximately 2%) concentrations of OXC were present in plasma. OXC was rapidly converted to a high extent to the 10-monohydroxy metabolite. MHD accounted for over 65% of the total AUC in plasma. The second metabolite CGP 10000 (trans dihydroxy derivative) was also present in low concentrations in plasma.

At therapeutic concentrations, OXC was moderately bound to serum proteins (76%), whereas binding of MHD was low (40%). Albumin was the major protein responsible for binding to serum proteins for OXC and MHD. Binding of OXC and MHD to gamma globulin and AAG was negligible.

Pharmacokinetic studies showed that following oral administration of Trileptal, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). After single dose administration of 600 mg Trileptal to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34µmol/L (8.65 µg/mL), with a corresponding median t_{max} of 4.5 hours. Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when Trileptal is given twice a day. At steady-state the pharmacokinetics of MHD are linear and show dose proportionality across the dose range of 300 to 2400 mg/day. Comparison of results from single dose pharmacokinetic studies to multiple dose studies indicated that there was a greater than 3-fold accumulation of MHD following multiple dosing.

Comparison of the pharmacokinetic parameters for MHD between young and elderly volunteers indicated that the exposure and peak concentrations of MHD were significantly higher (30 to 60%) in the elderly compared to young volunteers, after multiple doses of OXC. Comparisons of creatinine clearance in young and elderly volunteers indicated that the difference was due to age-related reductions in creatinine clearance.

respectively. These differences in CBZ, VPA and PHT exposures are probably not clinically significant.

Co-administration of Trileptal with an oral contraceptive has been shown to have an influence on the plasma levels of the two oral contraceptive components, ethinyl estradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE and LNG were decreased by [redacted] respectively. Therefore, concurrent use of Trileptal with hormonal contraceptives may render these contraceptives less effective. After repeated co-administration of Trileptal, the AUC values of felodipine were lowered by 28%. However the plasma levels remained in the recommended therapeutic range [redacted] On the other hand, verapamil produced a decrease of 20% of the plasma levels of MHD. This decrease in plasma levels of MHD is not considered to be of clinical relevance. Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, whereas viloxazine produced minor changes in MHD plasma levels (about 10% higher after repeated co-administration). Results with warfarin showed no evidence of interaction (no effect on prothrombin time) with either single or repeated doses of Trileptal.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed NDA 21-014 (Oxcarbazepine (Trileptal™) submitted on September 25, 1998. The overall Human Pharmacokinetics Section is acceptable. This recommendation, comments (pages 33) and labeling comments (pages 33-34) should be sent to the applicant as appropriate.

BACKGROUND

This review contains a summary of the studies submitted to the Human Pharmacokinetics and Bioavailability section in support of NDA 21-014. Individual study reports, including data, are on file in HFD-860 (Division of Pharmaceutical Evaluation I). The applicant is seeking approval of oxcarbazepine (Trileptal™) oral tablets (150, 300 and 600 mg tablets) in the USA.

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently registered in 47 countries. OXC is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active. Formation of MHD is stereospecific with 2 enantiomers formed in the ratio of 80% (S-MHD) and 20% (R-MHD), both of which have similar activity. The anticonvulsant properties of OXC and MHD are possibly mediated by blocking voltage dependant sodium channels, decreasing high voltage activated calcium channels and interaction with potassium channels. The blockade of voltage dependant sodium channels in the brain has been proposed as the most plausible mechanism of action. This is based on results from: 1) in-vitro studies in which OXC and MHD limited sustained high frequency repetitive firing of sodium-dependant action potentials of cultured mouse neurons, and 2) in-vivc study (maximal electroshock) which evaluates the ability of drugs to prevent electrically induced tonic hind limb extension seizures in rodents. Efficacy in the maximal electroshock model has shown to correlate with the ability to prevent partial and generalized tonic-clonic seizures in humans; also drugs that are active in this test (e.g. carbamazepine, phenytoin) often interact with voltage dependant sodium channels. OXC is indicated as a first-line anticonvulsant drug for the treatment of partial seizures (simple, complex and partial seizures evolving to secondary generalized seizures) in adults and children. The drug is proposed for use as monotherapy or as adjunctive therapy.

BIOANALYTICAL METHODS TO MEASURE OXC AND MHD IN PLASMA

[redacted]

CLINICAL PHARMACOLOGY

IN-VITRO DISTRIBUTION STUDIES

Protein binding: At therapeutic concentrations, OXC was moderately bound to serum proteins (76%), whereas binding of MHD was low (40%). The free fraction of both compounds, OXC and MHD increased at higher concentrations (MHD: 40.4% bound at 10 μg/ml and 28.6% bound at 100 μg/ml; OXC 68% bound at 10 μg/ml and 58.5% bound at 20 μg/ml).The protein binding of OXC was slightly influenced by MHD, the binding of MHD was not affected by OXC. The inter-subject variability was low for both OXC and MHD. Albumin was the major protein responsible for binding to serum proteins for OXC and MHD. Binding of OXC and MHD to gamma globulin and AAG was negligible. The binding of OXC and MHD to erythrocytes was constant up to concentrations of 20 and 25 μg/ml of OXC and MHD, respectively. The concentrations of OXC and MHD were higher in erythrocytes than in plasma (erythrocyte-to-plasma ratio =1.8 and 1.9 for MHD and OXC, respectively).

MASS BALANCE: A single dose study in two healthy volunteers using 400 mg [14-C]OXC were done to characterize the routes of excretion and metabolism of OXC. Two healthy males received a single oral 400 mg dose of [14-C]OXC, as solid substance in a gelatin capsule. The total administered radioactivity was 96.4 μCi in each volunteer. Blood samples were collected prior to dosing, and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 168 hours post dose. Urine and feces were collected at 24-hour intervals for up to 10 days.

Within the first day after dosing, approximately 57% of the dose was recovered in urine and feces (predominantly in urine). Elimination was essentially complete at 6 days post-dose. In both volunteers, most of the dose (over 94%) was renally excreted and less than 5% was excreted in the feces. This suggests that OXC is almost completely absorbed from the gastrointestinal tract. Maximum plasma concentrations of total radioactivity were reached 4 hours post-dose. Only low (approximately 2%) concentrations of OXC were present in plasma. OXC was rapidly converted to a high extent to the monohydroxy (MHD) metabolite. MHD accounted for over 65% of the total AUC in both subjects. The second metabolite CGP 10000 (trans dihydroxy derivative) was also present in low concentrations in plasma. Plasma concentrations of OXC were below 0.01 μg/ml 48 hours post-dose whereas MHD was still present in considerable amounts (0.5 μg/ml).

Characterization of the excretion products in urine showed that the most prominent metabolite in urine was MHD which accounted for 49% and 61% of the total urinary radioactivity in each subject. OXC was present in small amounts in urine (7.7% and 10.9%, respectively in each subject). CGP 10000 was also present in small amounts in urine (6.7% and 2.3%, respectively in each subject). Therefore, 3 compounds, intact OXC, MHD, and the trans dihydroxy derivative were recovered in urine of both volunteers; these accounted for 63.6% and 74.1% of the total radioactivity, respectively.

PHARMACOKINETICS (PK)

- What is the pharmacokinetic behavior of OXC in healthy subjects and in epileptic patients?
- Are the pharmacokinetics in epileptic patients similar to those in healthy volunteers?
- Are the pharmacokinetics different between males and females (effect of gender)?
- Are the pharmacokinetics different between young adults and the elderly? (effect of age)?

Following oral administration of OXC, the major metabolite excreted in urine were the glucuronide conjugates of S- and R-MHD; approximately 44% of the oral dose was excreted in urine as glucuronide conjugates. The glucuronide of S-MHD was present to a greater extent than that of R-MHD. Unchanged MHD was also renally excreted (27%); OXC was scarcely excreted in urine and DHD was renally excreted to a minor extent (2.7% of the dose).

A single dose pharmacokinetic study of OXC in 12 healthy young female volunteers was conducted. The objectives of the trial were to determine the pharmacokinetics of MHD after a single dose of 600 mg OXC in healthy young females. Doses were given after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following A Single 600 Mg Dose Of (N=12)

PK Parameters	Single dose
C_{max} (µg/mL)	5.17 (0.98)
T_{max} (h)	Median = 4.0
T1/2 (h)	16.1 (3.9)
AUCinf	135.4 (30.5)
AUCT	N/a
Amt. excreted in urine (0-96 h) (mg)	169.3 (45.2)
Amt. excreted in urine (240-252 h) (mg)	N/a

The PK parameters for MHD obtained in young females were similar to those obtained in an earlier single dose study in healthy males and females.

A single dose pharmacokinetic study of OXC in 12 healthy elderly female volunteers was conducted. The objectives of the trial were to determine the pharmacokinetics of MHD after a single dose of 600 mg OXC in healthy elderly females. Doses were given after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following A Single 600 Mg Dose Of OXC (N=12)

PK Parameters	Single dose
C_{max} (µg/mL)	7.20 (1.58)
T_{max} (h)	Median = 5.0
T1/2 (h)	24.2 (13.8)
AUCinf	221.6 (40.6)
AUCT	N/a
Amt. excreted in urine (0-96 h) (mg)	172.6 (33.3)
Amt. excreted in urine (240-252 h) (mg)	N/a

The pharmacokinetic data for MHD in elderly females was compared to the data obtained from a study in young healthy volunteers given the same dose of OXC. The C_{max} and AUC for MHD appear to be higher and t1/2 for MHD seems to be longer in elderly females compared to young subjects after a single 600 mg dose of OXC.

A single dose pharmacokinetic study of OXC in healthy young and elderly male volunteers was conducted. The study was open label; OXC was administered as a single 300 mg dose. Doses were administered after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Males Following A Single 300 Mg Dose Of OXC (N=12)

PK Parameters	Single Dose (Elderly)	Single dose (Young)
C_{max} (µg/mL)	2.88 (0.33)	2.33 (0.38)
T_{max} (h)	Median=5	Median=4
T1/2 (h)	19.3 (4.1)	13.9 (3.3)
AUC_{inf}	85.0 (14.4)	56.1 (13.7)

Statistical analysis comparing the pharmacokinetic parameters for MHD between the young and the elderly males indicated that the exposure and peak concentrations of MHD were significantly higher in the elderly compared to young volunteers, after a single dose of OXC. The elimination rate constant was also significantly different (smaller) in the elderly, resulting in a longer terminal half-life compared to that in young subjects. The applicant has related average K_{el} in each subject to the corresponding creatinine clearance (for young and elderly). The resulting graph suggests a

elimination half-life of MHD was similar following single and multiple doses of OXC. The dose corrected AUCT following multiple doses is larger than AUCinf following a single dose, suggesting that accumulation is greater than that expected for a drug exhibiting dose-proportional pharmacokinetics. A similar pattern was observed for the amount of MHD excreted in urine. The % of OXC dose recovered in urine as MHD ranged from [redacted] (mean = 45%).

A multiple dose pharmacokinetic study of 300 mg bid OXC in 12 healthy elderly female volunteers was conducted. Doses were administered after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following Multiple Doses (150 Mg Bid For One Day Followed By 300 Mg Bid For 4.5 Days In Healthy, Elderly Females (N=12)

PK Parameters	Multiple dose
C_{max} (µg/mL)	11.72 (1.97)
T_{max} (h)	Median = 3.0
T1/2 (h)	16.5 (2.8)
AUCT	121.9 (20.2)
Amt. excreted in urine (240-252 h) (mg)	115.8 (19.0)

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The inter-individual variability in the pharmacokinetic parameters for MHD was relatively small. Comparison to results from the single dose component of this study (see previous page) was done. The results on Cmax (after correcting for dose) indicate that there was a greater than 3-fold accumulation of MHD following multiple dosing. Statistical analysis indicated that Tmax occurred earlier following multiple doses compared to Tmax following a single dose. The elimination half-life of MHD following multiple doses of OXC was shorter than that following a single dose, suggesting that some induction of the elimination process may occur during multiple dosing. The dose corrected AUCT following multiple doses was slightly larger than AUCinf following a single dose, suggesting that accumulation is greater than that expected for a drug exhibiting dose-proportional pharmacokinetics. A similar pattern was observed for the amount of MHD excreted in urine. The % of OXC dose recovered in urine as MHD ranged from [redacted] (mean = 43%).

The pharmacokinetic data for MHD in elderly females was compared to the data obtained from a study in young healthy volunteers given the same dose(s) of OXC. The C_{max} and AUC appear to be higher (23% and 33%, respectively) and t1/2 for MHD seems to be longer (15%) in elderly females compared to young subjects, after multiple dosing.

A multiple dose (300 mg bid of OXC) pharmacokinetic study of Trileptal in healthy young and elderly male volunteers was conducted. Doses were administered after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Males Following Multiple Doses (300 Mg Bid For 7.5 Days (N=12)

PK Parameters	Multiple dose (Elderly)	Multiple dose (Young)
C_{max} (µg/mL)	12.03 (1.21)	8.49 (1.98)
T_{max} (h)	Median=4	Median=2
T1/2 (h)	26.5 (6.7)	14.2 (3.4)
AUCT	132.7 (14.9)	86.8 (19.0)

Statistical analysis comparing the pharmacokinetic parameters for MHD between the young and the elderly males indicated that the exposure and peak concentrations of MHD were significantly higher (approx 50%, in each case) in the elderly compared to young volunteers, after multiple doses of OXC. The elimination rate constant was also significantly different (smaller) in the elderly, resulting in a longer terminal half-life (almost 2-fold greater) compared to that in young subjects. The applicant has related average K_{el} in each subject to the corresponding creatinine clearance (for young and elderly). The resulting graph suggests a positive correlation when all subjects were used in the regression analysis. However, within either age group, there was no significant correlation between K_{el} and creatinine clearance. The higher peak concentrations and exposure and the lower Kel in the elderly subjects suggests a lower clearance of MHD in this age group. Since MHD is mainly glucuronidated and excreted in the urine, the differences observed may be due the difference in creatinine clearance (renal function) between the elderly and the

OXC 600 mg (2x300 mg) in comparison with PB 66 mg and placebo on cognitive function. The study was a double blind, 3-period, crossover comparison of OXC with PB and placebo in 22 healthy adult (12 males and 10 females) volunteers. There was a washout period of 9 days between study periods. Volunteers were administered study medication following a breakfast meal. The following pharmacodynamic endpoints were measured predose (0 hr) and 2, 4, 7, and 24 hours post-dose: Simple reaction time test, binary reaction time test, finger tapping test, computerized visual searching test, recognition test.

Statistical analysis was done to compare OXC and PB for treatment differences and PB versus placebo to test the sensitivity of the trial. Confirmatory analysis was performed for the reaction time tests and recognition task using an analysis of covariance appropriate for a 3-period crossover study. The baseline of each treatment period was used as a covariate in the analysis. As part of exploratory analyses, a summary measure (AUC0-24) was obtained for the simple reaction test and recognition task and these values were analyzed using an analysis of variance appropriate for a 3-period crossover study. Statistical analysis showed no significant differences between the 3 treatments in any of the primary measures for the pharmacodynamic tests. No clinically relevant differences in cognitive function were observed in healthy volunteers following single doses of 600 mg OXC, 66 mg PB or placebo. This may be due to the low doses of test drugs used in the study, the single dose nature of the study or to the poor sensitivity of the test battery in healthy volunteers.

A multicenter, randomized, double blind, placebo-controlled, parallel, add-on trial of oxcarbazepine (OXC) was conducted to evaluate the safety and efficacy of OXC, as adjunctive therapy, relative to placebo in children (4-17 years) with inadequately controlled partial seizures. A secondary objective of this trial was to explore the pharmacokinetic-pharmacodynamic (efficacy and safety) relationships of OXC in the pediatric population, as well as explore the drug-drug interaction potential of OXC when given with other antiepileptic drugs (AEDs). The study design allowed patients with inadequate seizure control to continue on a stable regimen of one or two AEDs, in addition to receiving OXC or placebo. The trial consisted of 3 phases:

Phase	Baseline		Double Blind Phase					
Period			Titration	Maintenance				
Visit	1	2	3	4	5	6	7	8
Day	-56 to -1	0	14	28	42	56	84	112
Treatment	1 – 2 AEDs		OXC or Placebo plus 1 – 2 AEDs					
	↑ randomization							

Titration period for OXC/placebo began between Visit 2 and 3 and lasted for 14 days. This was followed by a 98 day maintenance period. The 14-day titration schedule is shown below.

Days	Dose (mg/kg/day, P.O.)
1 – 2	10
3 – 6	20
7 - 10	30
11 – 14	Randomized dose or max. tolerated dose (whichever was less)

Based on the body weights recorded at Visit 2, the patients' target randomized trial drug doses were determined on a mg/kg basis, based on weight categories:

Body weight on Visit 2	Target randomized Daily Dose
20 – 29.0 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 – 39.0 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 – 60.0 kg	1800 mg (30 mg/kg to 46 mg/kg)
Body weights of greater than 60 kg were randomized to the 1800 mg dose.	

The primary efficacy variable, % change in 28-day seizure frequency relative to baseline was fit to a regression model. The % change in 28-day seizure frequency relative to baseline was significantly related to treatment group or C_{min} ($p<0.001$ for each), using baseline seizure frequency as a covariate. However, R-squared and root mean square error were not significantly different for the different pharmacokinetic-efficacy models.

Relationships between Cmin and the AEs (and clinical labs) were explored. Based on statistical significance, patients with higher Cmin were associated with higher incidences than the patients on placebo for ataxia, diplopia, dizziness, headache, nausea, somnolence and vomiting (however, scatter plots do not suggest a clear relationship between Cmin and the incidence of any of the observed AEs).

The safety and efficacy of 1200 mg/day of OXC was conducted to evaluate the safety and efficacy of OXC monotherapy relative to placebo in untreated patients with recent onset partial seizures. A secondary objective of this trial was to explore the pharmacokinetic-pharmacodynamic (efficacy and safety) relationships in OXC monotherapy. The study was a multicenter, double blind, randomized, placebo controlled, parallel group trial to investigate the safety and efficacy of OXC monotherapy (1200 mg/day) compared to placebo in patients (10 years or older) who were not receiving antiepileptic drug (AED) therapy for partial seizures.

Phase	Baseline		Double Blind Phase				
Period			Titration	Maintenance			
Visit		1	2	3	4	5	6
Day	-56	-7 to 1	0	7	35	63	91
Treatment	NO AEDs for 90 days		Placebo or gradual titration to OXC 1200 mg/day				
	↑ randomization						

Titration period for OXC/placebo began on Visit 2. Patients randomized to OXC treatment were started on an initial OXC dose of 600 mg/day (300 mg bid) on days 1 and 2 and were titrated to 900 mg/day (450 mg bid) on days 3 and 4 and 1200 mg/day (days 5 and 6). Patients randomized to the placebo treatment received matching placebo tablets throughout the double blind phase. The maintenance period lasted for 84 days during which patients received OXC 1200 mg/day or placebo. Patients who were unable to tolerate the 1200 mg/day OXC dose were allowed to have their dose decreased to 900 mg/day at Visit 3 only.

Blood samples were collected at Visits 3 to 6 for population pharmacokinetic-pharmacodynamic analysis of plasma levels of OXC and MHD. Patients were required to record the time of their last 3 doses and the time of their last meal prior to the visit. To ensure that blood samples were collected evenly during the visit, the 8:00 am to 6:00 pm time period was divided into 3 time slots (8:00 am to 11:00 am, 11:01 am to 2:00 pm, 2:01 pm to 6:00 pm). Patients were required to report for their blood draws at each of the 3 time slots (in any order) at least once during visits 3-6. The purpose of the schedule was to distribute blood samples over the drug absorption and elimination phases. At one center, blood samples were collected (Visits 3-6) just before the morning dose for determination of trough concentrations of OXC and MHD.

Non linear mixed effects models were fitted to the plasma concentrations of MHD using NONMEM Version 4. The analysis procedure for the pharmacokinetic model was similar to that described in the section above.

To explore pharmacokinetic-efficacy relationships, Cmin was used as an explanatory variable in regression models for the primary outcome – time to first seizure. The models fitted to the data were of the form: $\text{Log}\,\lambda\,(t) = a_0 + \beta_1 SEIZB\_28 + \beta_2 TRT + \beta_3 Cmin$, where, $\lambda\,(t)$ is the hazard rate for the time to first seizure at time t, SEIZB_28 is he 28-day baseline seizure frequency, TRT is the treatment group (placebo=0 or OXC 1200 mg/day=1), a_0 is the natural logarithm of the baseline hazard (hazard rate for a hypothetical patient with SEIZB_28 = Cmin = TRT =0) and β_0, β_1, β_2, β_3 are regression parameters.

$C_{max,\ spec}$, $AUC_{inf,\ spec}$ = Specific values of Cmax and AUC for a dose unit, i.e, values of Cmax and AUC adjusted for the actual dose, divided by the theoretical dose 5 or 15 mg/kg and multiplied by the conversion factor (0.2523) for dose in molar units.

MHD was the main active compound in plasma in children dosed with 5 or 15 mg/kg OXC. OXC concentrations were low; approximately [redacted] of MHD concentrations (similar to adults). The pharmacokinetics of MHD were age-dependant with lower exposures and shorter t1/2 observed in the younger group (2-5 years) compared to the older group (6-12 years). Peak MHD concentrations increased less than proportionally with dose and mean values of $C_{max,spec}$ decreased significantly with increasing dose in both age groups. This was not observed in adults following single doses of 150, 300 and 600 mg OXC. The lower exposure of MHD observed in the younger children (2-5 years) maybe partly related to faster metabolism in this age group as compared to adults or children between the ages of 6-12 years. The pharmacokinetic parameters for MHD from this study have been compared to those obtained in adults. The mean T1/2 of MHD in children aged 6-12 years receiving 15 mg/kg (9 hours) was similar to that in healthy adults (9-10 hours) following administration of OXC. The mean t1/2 in the age group 2-5 years at both doses and in the age group 6-12 years at the 15 mg/kg dose was lower than that observed in adults. Comparison of the MHD exposure ($AUC_{inf,\ spec}$) between children and adults showed that the MHD exposure was similar between adults (lowest mean value observed in adults)and children aged 6-12 years; the exposure in children aged 2-5 years was lower.

Multiple dose pharmacokinetics following treatment with tid (or bid) OXC in children on concomitant anticonvulsant drugs: The trial was a multicenter study divided in 3 periods: titration, maintenance and follow-up in which epileptic children with upto 3 anticonvulsant drugs received OXC in addition. Children were divided into 2 groups based on age: 2-5 and 6-14 years.
Titration period: 2 months, visits 1-4. Each patient received a starting dose of OXC of about 10 mg/kg/day. The dose was then increased progressively in order to obtain satisfactory safety and efficacy.
Maintenance Period: 4 months, visits 5-7. Once the optimal dose was determined, patient who showed therapeutic benefit entered this phase. Change of the dosing regimen due to insufficient therapeutic effect and/or poor tolerability was exceptionally allowed. Also, doses greater than 50 mg/kg were exceptionally allowed.
Follow-up Period: 1 year, visits 8 and 9. During this long term follow-up period, the dosing regimen could be modified and doses greater than 50 mg/day were exceptionally allowed.
Blood samples were collected from visits 1-7 (titration and maintenance) and in some patients at visit 9 (follow-up) in the morning before administration of OXC for the determination of MHD. The study population consisted of 114 epileptic children with partial or generalized tonic-clonic seizures. Children were divided into 2 groups based on age: 2-5 years and 6-14 years . Of these 85 patients were included in the statistical analysis. The mean specific optimal dose in children aged 2-5 years was 38% higher than in children aged 6-14 years [redacted]
Since the difference is small compared to the range of doses used across age groups, age may be a minor factor for adjustment of the effective dose of OXC. MHD trough concentrations were lower (average of 34%) in younger children compared to the older age group. This indicated a more rapid elimination of MHD in younger children. Concomitant AED's with enzyme inducing properties decreased MHD trough concentrations by 12% and 32% in the younger and older age groups, respectively.

Multiple dose pharmacokinetics following treatment with tid (or bid) OXC in children treated with upto 2 antiepileptic drugs (after substitution of Tegretol therapy): The study was an open label trial in 22 children who were being treated with Tegretol for epilepsy. Tegretol was gradually replaced with OXC. During the titration phase (4–8 weeks), the daily dose of OXC was individually adjusted at weekly intervals in order to obtain the maximum therapeutic benefit along with satisfactory tolerability. Once the optimum maintenance dose was identified, the treatment was continued for at least 12 weeks. Blood samples were collected before the morning dose during the titration phase (maximum of 9 samples in weekly intervals) and during the maintenance phase (4 samples in 2-4 week intervals). The maximum therapeutic benefit associated with a satisfactory tolerability was reached in this group of 22 patients with a mean daily OXC dose of 1200 mg ± 444 mg, resulting in mean steady-state MHD concentrations of 56.8 ±22.8 nmol/g. The daily dose of OXC increased with increase in patient age and weight. There appeared to be no relationship between the MHD steady-state concentrations and

from 24-77 years, with a body weight from 49 to 89 kg. Subjects were classified into one of 4 groups based on their creatinine clearance:
Group 1: Clcr > 90 ml/min (n=6); healthy subjects; Group 2: Clcr 30 – 80 ml/min (n=6)
Group 3: Clcr 10 – 30 ml/min (n=7) and Group 4: Clcr 2 – 10 ml/min (n=7); not hemodialyzed.

Mean (SD) Plasma Pharmacokinetic Parameters for Unconjugated MHD, OXC and DHD

PK parameter	Group 1:Clcr > 90 ml/min (n=6)	Group 2: Clcr 30 – 80 ml/min (n=6)	Group 3: Clcr 10 – 30 ml/min (n=7)	Group 4: Clcr 2 – 10 ml/min (n=7)
MHD Pharmacokinetics				
Cmax (μmol/l)	8.6 (0.8)	12.1 (2.3)	13.7 (3.4)	13.0 (2.7)
Tmax (hr); median	4	6	8	6
AUCinf (μmol.h/l)	203 (37)	337 (74)	502 (167)	491 (113)
T1/2 (hr)	10 (1)	12 (2)	16 (5)	19 (3)
OXC Pharmacokinetics				
Cmax (μmol/l)	1.23 (0.45)	1.67 (0.90)	1.45 (0.59)	1.82 (1.50)
Tmax (hr); median	1.5	2	2	2
AUC0-168 (μmol.h/l)	4.2 (1.3)	7.9 (4.6)	9.2 (5.5)	8.3 (3.2)
DHD Pharmacokinetics				
Cmax (μmol/l)	0.18 (0.04)	0.34 (0.07)	0.48 (0.13)	0.49 (0.20)
Tmax (hr); median	12	24	48	42
AUC0-168 (μmol.h/l)	4.8 (3.0)	24.8 (12.9)	44.0 (16.5)	51.4 (23.7)

Peak plasma MHD concentrations in patients with impaired renal function were higher than those in normal volunteers. The half-life for MHD increased with degree of renal impairment, with the longest mean terminal half-life for Group 4. The MHD exposure was 1.5 times greater for Group 2 compared to Group 1 and approximately 2.5 times greater for Groups 3 and 4 compared to Group 1. Exposure to MHD and peak MHD concentrations were similar for Groups 3 and 4. OXC exposure was approximately 2-fold greater in patients with renal impairment compared to normal volunteers. The influence of renal impairment on the plasma levels of DHD was marked. In subjects with normal renal function, maximum plasma DHD concentrations were reached approximately 12 hours post-dose. For patients with impaired renal function, maximum plasma MHD concentrations following dosing were reached after 24 hr for Group 2, 48 hours for Group 3 and 42 hours for Group 4. Peak plasma DHD concentrations in patients with impaired renal function were 2.5 fold greater than those in normal volunteers. The DHD exposure was 5-6 fold greater for Group 2 compared to Group 1 and approximately 10 fold greater for Groups 3 and 4 compared to Group 1. Exposure to DHD and peak DHD concentrations were similar for Groups 3 and 4. The results suggest that oxidation of MHD to DHD was enhanced in patients with renal impairment, suggesting that metabolism by the liver may compensate for renal impairment.

The relationship between the exposure to MHD, OXC and DHD following OXC administration and creatinine clearance was explored. Results suggested that MHD and DHD exposures are increased in subjects with low serum creatinine clearance values. The concentrations of conjugated MHD and OXC were expressed as the difference between concentrations determined before and after hydrolysis. For DHD, the total concentrations measured after hydrolysis was similar to those of the unconjugated compound, indicating that the concentrations of conjugated DHD were low.

Mean (SD) Plasma Pharmacokinetic Parameters for Conjugated MHD, OXC and DHD

PK parameter	Group 1:Clcr > 90 ml/min (n=6)	Group 2: Clcr 30 – 80 ml/min (n=6)	Group 3: Clcr 10 – 30 ml/min (n=7)	Group 4: Clcr 2 – 10 ml/min (n=7)
MHD Pharmacokinetics				
Cmax (μmol/l)	2.1 (0.7)	4.4 (2.8)	10.8 (3.4)	19.9 (6.7)
Tmax (hr); median	8	10	32	32
AUCinf (μmol.h/l)	48.7 (9.9)	176 (138)	731 (342)	1770 (914)
T1/2 (hr)	13 (3)	14 (5)	24 (9)	42 (25)
OXC Pharmacokinetics				
Cmax (μmol/l)	1.3 (0.7)	2.2 (0.8)	4.1 (3.3)	5.5 (2.1)
Tmax (hr); median	1.5	4	8	10
AUC0-168 (μmol.h/l)	11.2 (4)	35.8 (18.7)	149 (107)	298 (77)
T1/2 (hrs)	-	18 (6)	16 (6)	43 (18)

mild HI (Child-Pugh classification A) and Group 3: moderate HI (Child-Pugh classification B). The study was conducted in 26 males ranging in age from 40 to 65 years, 12 with normal hepatic function, 7 with mild HI and 7 with moderate HI. Of these, pharmacokinetic evaluations were performed in 6 healthy volunteers, 7 mildly impaired and 6 moderately impaired patients. OXC was administered following administration of a standardized breakfast.

Mean (SD) MHD Plasma Pharmacokinetic Parameters

PK Parameter	Group 1 (n=6) Normal	Group 2 (n=7) Child-Pugh A	Group 3 (n=6) Child-Pugh B
AUC0-24 (μmol.h/l)	1094.3 (274.7)	1189.1 (185.4)	1026.8 (148.1)
AUCinf (μmol.h/l)	1112.5 (272.5)	1207.9 (189.7)	1044.3 (148.7)
Cmax (μmol/l)	41.2 (8.8)	43.6 (4.4)	35.8 (3.2)
Tmax (h)	8 (median)	8 (median)	10 (median)
T1/2 (hr)	10.4 (1.8)	10.5 (1.2)	12.2 (1.3)

Mean (SD) DHD Plasma Pharmacokinetic Parameters

PK Parameter	Group 1 (n=6) Normal	Group 2 (n=7) Child-Pugh A	Group 3 (n=6) Child-Pugh B
Cmax (μmol/l)	1.0 (0.5)	0.4 (0.3)	0.4 (0.5)
Tmax (h)	24 (median)	24 (median)	24 (median)

There were no statistically significant differences in the AUC and Cmax for MHD between normal volunteers and subjects with mild or moderate HI. DHD levels were close to or below the limit of quantitation for most subjects at several time points; therefore, no other pharmacokinetic parameters were calculated for DHD in plasma. For DHD, the difference in Cmax between normals and hepatically impaired subjects was statistically significant (lower). The baseline hepatic function classification on the Cmax for DHD was statistically significant.

90% confidence intervals for the ratios of AUC and Cmax (for MHD) between mildly impaired and moderately impaired groups and for the normal subjects were estimated. The results suggest that in patients with mild HI, the MHD exposure and peak MHD plasma concentrations were slightly higher than those in patients normal hepatic function. There did not appear to be any differences between patients with moderate hepatic impairment and normal volunteers.

Parameter	Pairwise comparison	Ratio	90% CI
AUCoo (μmol.h/l)	Child Pugh A (mild) vs Normal	1.105	(0.92, 1.33)
	Child Pugh B (moderate) vs Normal	0.957	(0.79, 1.16)
Cmax (μmol/l)	Child Pugh A (mild) vs Normal	1.075	(0.93, 1.24)
	Child Pugh B (moderate) vs Normal	0.884	(0.76, 1.03)

Mean (SD) Urine Pharmacokinetics for MHD

Parameter	Compound	Normals (n=6)	Child-Pugh A (n=7)	Child-Pugh B (n=6)
Ae (0-120 h) (% of dose)	Free MHD	17.0 (14.1)	27.6 (17.1)	19.5 (8.3)
Ae (0-120 h) (% of dose)	Conjugated MHD	22.4 (4.1)	23.6 (8.7)	14.7 (7.6)
Ae (0-120 h) (% of dose)	Total MHD	39.4 (16.0)	51.2 (24.6)	34.2 (15.5)
Renal Clearance (L/h)	Free MHD	0.51 (0.32)	0.85 (0.58)	0.69 (0.34)

Mean (SD) Urine Pharmacokinetics for DHD

Parameter	Compound	Normals (n=6)	Child-Pugh A (n=7)	Child-Pugh B (n=6)
Ae (0-120 h) (% of dose)	Free DHD	1.6 (1.3)	1.5 (1.3)	1.1 (1.4)
Ae (0-120 h) (% of dose)	Total DHD	2.3 (0.9)	2.0 (1.1)	1.4 (2.2)

The amounts of free, conjugated and total MHD excreted in the first 120 hours after dosing (Ae0-120) were expressed as a percent of the dose. The urinary excretion of free, conjugated and total MHD was similar for all three groups. The urinary excretion rates were also similar across groups. There were no significant differences in the renal clearance of MHD between the 3 hepatic function groups. For DHD, the urinary excretion of free and total DHD tended to decrease with the severity of hepatic impairment, however, the interindividual variability was high.

are not likely to be clinically relevant, and as this ratio approaches or increases beyond unity, the potential for drug interactions increases.

Results from these experiments suggested that OXC and MHD have little capacity to inhibit most of the P450 enzymes with the exception of CYP 2C19 and CYP 3A4/5. Both OXC and MHD were observed to competitively inhibit CYP 2C19 with Ki values of 228 μM and 88μM, respectively. CYP 3A4/5 was found to be inhibited both by OXC (non-competitive) and MHD (competitive) at Ki values of 279 μM and 647 μM, respectively. The mean steady state trough plasma concentrations of MHD following 1200 mg bid dose of OXC is approximately 108 μM in patients and C_{max} following a 1200 mg dose was approximately 50 μM. Comparing these pharmacokinetic parameters to the Ki values suggest that while inhibition of CYP 3A4/4 by OXC and MHD may not have clinical significance, the inhibition of CYP 2C19 substrates by OXC and MHD may be clinically relevant.

OXC & MHD as competitive inhibitors of P450 enzymes in human liver microsomes

P 450 enzyme	P 450 activity	Competitive Inhibition by OXC		Competitive Inhibition by MHD	
		Ki (μM)	Cmax /Ki	Ki (μM)	Cmax /Ki
CYP 1A2	7-Ethoxyresorufin O-dealkylase	1150	0.0043	> 1350	0.037
CYP 2A6	Coumarin 7-hydroxylase	>1350	< 0.0037	> 1350	0.037
CYP 2C9	Tolbutamide methyl-hydroxylase	> 1350	< 0.0037	> 1350	0.037
CYP 2C19	S-mephenytoin 4'-hydroxylase	228	0.022	88.3	0.57
CYP 2D6	Dextromethorphan O-demethylase	> 1800	< 0.0028	> 1800	0.028
CYP 2E1	Chlorzoxazone 6-hydroxylase	> 900	< 0.0056	> 900	0.056
CYP 3A4/5	Testosterone 6 -hydroxylase	270	0.019	647	0.077
CYP 4A9/11	Lauric Acid 12-hydroxylase	> 1350	< 0.0037	> 1350	0.037

Cmax for OXC = 5 μM; Cmax for MHD = 50 μM

In-vitro induction of CYP P450 enzymes: The effects of OXC, MHD and DHD on CYP P450 enzymes was studied in vitro using human hepatocytes. Phenobarbital and rifampicin were used as reference compounds. OXC, MHD and DHD at concentrations of 50 and 200 μM and phenobarbital at 3000 μM and rifampicin at 50 μM were incubated with adult female human hepatocytes in primary culture. Induction by OXC and MHD of Ethoxyresorufin O-dealkylase (EROD) and pentoxyresorfin O-dealkylase (PEROD), two CYP dependant drug metabolizing enzyme activities were evaluated. Also, methylumbelliferone conjugation with glucuronic acid was studies to evaluate the inductive effects of OXC and MHD on Phase 2 glucuronidation.

A 3.2 fold decrease in EROD activity was found during the 72-hour incubation period in the control cultures. In comparison, 69% and 60% increases were observed with DHD (at 200 μM) and rifampicin, respectively. A 1.6 fold decrease in PEROD activity was found during the 72-hour incubation period in the control cultures. In comparison, approximately a 30-34% increase was observed with OXC (at 50 and 200 μM) and phenobarbital. UDP-glucuronyltransferase activity was well maintained throughout the 72-hour incubation period. It was increased 1.2 to 1.5 fold by all test compounds as well as the reference substances. The highest increase obtained was observed with OXC (47%). MHD and DHD showed lower effects (22% and 39%, respectively).

To summarize, these results showed that EROD activity (CYP activity) was slightly increased after a 72-hour exposure to DHD, compared to control cultures and UDP-glucuronyltransferase activity was induced by OXC, DHD and MHD.

IN-VIVO METABOLISM: Studies with carbamazepine (CBZ) have shown that there is a change in antipyrine kinetics during CBZ treatment, suggesting enzyme induction by CBZ. Since OXC is an analog of CBZ, this trial was aimed at obtaining additional information on the hepatic oxidative enzyme inducing potential of OXC in a population maintained at a high daily dosage of OXC. Antipyrine was used as a marker to determine the oxidizing capacity of CYP P450 enzymes.

A pharmacokinetic study on the enzyme-inducing capacity of OXC was conducted in healthy males following multiple, oral doses. The study was an open label study with 3 sequential treatments given to each subject. Treatment A=1x600 mg antipyrine given orally;

single center, within-volunteer trial consisting of 2 periods: a treatment period and a treatment-free period.

Treatment Period:

Day 1: Subjects received a single dose of 18 mg/kg oral antipyrine only (baseline; visit 1);
Days 2-13: Subjects received 300 mg qd OXC on days 2-3, 300 mg bid OXC on days 4-5; 450 mg bid on days 6-7; 600 mg bid on days 8-10 and 750 mg bid on days 11-13;
Day 14: Subjects reached the maintenance dose of 900 mg bid OXC (visit 2);
Day 21: Subjects come in for visit 3;
Day 14-35: Subjects continued with the maintenance dose of 900 mg bid OXC. At the end of the maintenance period, on Day 35, subjects received a single dose of 18 mg/kg oral antipyrine (visit 4).

Treatment-free period: consisted of 4 weeks. At the end of 4 weeks of no treatment, subjects received a single dose of 18 mg/kg oral antipyrine only (visit 5).

300 mg uncoated tablets of OXC (formulation f4, batch number 003400) were used.

Mean (SD) Pharmacokinetic Parameters for Antipyrine (n=13)

Parameters	Visit 1 Before treatment with OXC	Visit 4 During treatment with OXC	Visit 5 After treatment with OXC
Body weight (kg)	67.4 (6.6)	67.4 (6.6)	67.4 (6.6)
C_{max} (µg/g)	25.4 (4.9)	24.1 (4.1)	25.4 (6.2)
T_{max} (h)	2	1	1
T1/2 (hr)	10.8 (3.2)	8.7 (2.1)	10.6 (3.2)
AUC0-24 (mg.h/L)	316.7 (86.9)	244.3 (58.1)	316.9 (91.2)
AUCoo (mg.h/L)*	418.2 (147.6)	293.3 (92.0)	413.2 (146.4)

* For visits 1 and 5, the extrapolated area to calculate AUCoo was > 20%.

The applicant has compared the half-life and AUC of antipyrine during treatment with OXC to those before and after treatment with OXC. The following ratios of the half-life (and AUC) of antipyrine were determined: Visit 4/Visit1, Visit4/Visit5, Visit 1/Visit 5. The estimated ratios were determined by fitting a general linear model to antipyrine half-life (AUC) on a log scale. The model included subject effect and treatment effect (before OXC, during OXC and after OXC). The 95% CI of the ratios were also calculated.

Comparison	Difference in means		P-value		Ratio		95% CI	
	T1/2	AUCoo	T1/2	AUCoo	T1/2	AUCoo	T1/2	AUCoo
Visit 4/Visit1 During vs Before	-0.20	-0.42	*0.03*	*0.0001*	0.82	0.66	(0.69, 0.98)	(0.55, 0.79)
Visit 4/Visit 5 During vs. After	-0.18	-0.32	*0.05*	*0.0013*	0.84	0.73	(0.70, 1.00)	(0.61, 0.87)
Visit 1/Visit 5 Before/After	0.02	0.10	0.82	0.27	1.02	1.11	(0.86, 1.21)	(0.92, 1.33)

The results suggest that the antipyrine half-life was decreased during treatment with OXC when compared to before (or after) treatment with OXC. OXC had an effect on antipyrine half-life in reducing it by 22%. Similar findings were observed with the effects of OXC on antipyrine exposure. The results revealed a statistically significant decrease in antipyrine half-life of 22% during administration of daily doses of 1800 mg. Treatment with OXC (1800 mg/day) has a moderate inducing effect on the P450 enzyme system. Comparison of trough levels of OXC and MHD during the different treatment periods suggest that there is no significant autoinduction in the metabolism of OXC following repeated doses of OXC.

An open label, placebo controlled trial was conducted to determine the effects of 900 mg bid OXC on markers of enzyme induction in healthy males nifedipine and antipyrine were used as markers). The study was an open label, single center, placebo controlled trial. The elimination half-lives of the enzyme markers, nifedipine and antipyrine, were determined prior to dosing with OXC/placebo on Days 1 and 3, respectively. On Day 5, subjects received a single 600 mg dose of OXC/placebo following a standard breakfast. From Day 12, subjects took OXC/placebo according to a fixed titration schedule. The titration period of 13 days consisted of: Days 12-15: 300 mg bid OXC; Days 16-19: 600 mg bid OXC; Days 20-23: 750 mg bid OXC.

that since the dose of OXC will be titrated in patients receiving CBZ or PHT if their seizures are not controlled, the lower MHD exposure following coadministration with CBZ/PHT is probably not clinically significant. However, the observed decreases in MHD AUC of 40% and 30% following coadministration with CBZ and PHT, respectively, must be clearly stated in the label to alert clinicians of the decrease in MHD exposure when OXC is administered with these two drugs.

Effects of phenobarbitone (PB) and sodium valproate (VPA) on the Pharmacokinetics of Oxcarbazepine: The study was designed to assess the pharmacokinetic profile of MHD after a single, oral dose of 600 mg in epileptic patients chronically treated with either VPA or PB monotherapy, in comparison with the pharmacokinetic profile of MHD after the same single dose in drug-free healthy subjects. The doses of PB ranged from 100-150 mg/day and the doses for VPA ranged from 1000-2000 mg/day. Patients on PB have approximately 30% lower plasma concentrations than healthy, drug-free subjects, as determined from the differences in AUC of MHD between the 2 groups. This suggests that MHD metabolism is induced by PB, resulting in lower concentrations of the former. MHD metabolism is therefore, moderately affected by PB coadministration. The pharmacokinetics of MHD between healthy, drug-free subjects and patients on VPA were not significantly different. These results suggest that VPA does not inhibit the enzymes involved in the glucuronidation of MHD.

Effects of Viloxazine on the Pharmacokinetics of Oxcarbazepine: The study was designed as a double blind, placebo-controlled, 2-treatment, crossover study in epileptic patients to assess the effects of repeated doses of viloxazine 100 mg bid for 10 days) on the pharmacokinetics of OXC (individualized regimen). All patients were on OXC monotherapy for at least one month preceding the trial. Plasma steady-state concentrations of unchanged OXC were not influenced by viloxazine coadministration. The concentrations of the major and pharmacologically active metabolite, MHD were approximately 10% higher after coadministration with viloxazine compared to those following OXC alone. Plasma concentrations of the pharmacologically inactive metabolite, DHD, decreased by approximately 31% following coadministration of OXC. These differences are small and probably not clinically significant .

Effects of Verapamil on the Pharmacokinetics of Oxcarbazepine: The study was designed as a non randomized, open label study in healthy males to assess the effects of a single (120 mg) and repeated doses of verapamil (120 mg bid for 7 days) on the steady-state pharmacokinetics of OXC (titration of OXC to a daily dose of 450 mg bid). The exposure to the main and pharmacologically active metabolite, MHD, following coadministration of OXC and of verapamil (single and multiple doses), was approximately 20% lower than the exposure following OXC alone. Lower exposure and Cmax (of approximately 50%, in each case) were obtained for the minor and inactive metabolite, DHD, following coadministration of OXC and verapamil (multiple doses). However, these differences, probably due to an inhibition of the oxidation of MHD, are probably not clinically relevant.

Effects of steady state erythromycin on the pharmacokinetics of OXC: The study was designed as an open label, randomized, crossover study in healthy volunteers to assess the effects of repeated doses of erythromycin (500 mg bid for 7 days) on the pharmacokinetics of a single dose OXC (600 mg). Results from the analysis showed that were no significant differences in MHD exposure and Cmax following coadmiistration with OXC. The bioavailability of the active metabolite, MHD is unchanged following coadministration with erythromycin.

Effects of steady state cimetidine on the pharmacokinetics of OXC: The study was designed as an open label, randomized, crossover study in healthy volunteers to assess the effects of repeated doses of cimetidine (400 mg bid for 7 days) on the pharmacokinetics of OXC (600 mg). Results from the analysis showed that were no significant differences in MHD exposure and Cmax following coadmiistration with OXC. The bioavailability of the active metabolite, MHD is unchanged following coadministration with cimetidine

The applicant conducted another study to assess the effects of multiple doses of OXC (1200 mg/day) on the steady state pharmacokinetics of two active ingredients of the oral contraceptive, Evanor-D, in healthy females. The active ingredients in the oral contraceptive were ethinyl estradiol (EE) and levonorgestrel (LNG). Progesterone trough concentrations were measured as a pharmacodynamic endpoint to evaluate the occurrence of ovulation. This study was conducted to confirm the findings in the earlier study using OXC and oral contraceptives, which showed that concentrations of EE and LNG were reduced significantly (48% and 32%, respectively) when coadministered with OXC. This study utilized higher doses of OXC as well as the oral contraceptive than the earlier study. Compared to the treatment with placebo, AUC values for EE and LNG were significantly lower during treatment with OXC (approximately 52% in each case). Mean Cmax values for EE and LNG were also decreased moderately during treatment with OXC when compared to placebo. The mean progesterone concentrations during the OXC treated and placebo phases of the study were 0.53 ± 0.32 and 0.55 ± 0.28 μmol/L, respectively. The similarity of progesterone trough concentrations suggests that the decrease in EE and LNG concentrations during OXC treatment did not result in a change in progesterone levels and hence trigger an ovulation. However, it was noted that two intermenstrual bleedings occurred during the trial during treatment with OXC (both in the same subject). Intermenstrual bleeding in this subject was interpreted clinically as a sign of contraceptive failure. This study also demonstrated that concomitant administration of OXC with oral contraceptives may not provide sufficient protection from conception. Female patients must therefore use alternate and additional forms of birth control when taking OXC.

Effects of single and repeated doses of OXC on the pharmacokinetics of felodipine:
Felodipine is a calcium antagonist used in the treatment of hypertension, angina pectoris and heart failure. Felodipine is metabolized by the microsomal cytochrome P-450 enzyme; interactions with drugs that are metabolized by the same enzymes may be anticipated. OXC is largely metabolized by non-oxidative processes. However, results from previous in-vitro and in-vivo studies with OXC that showed that OXC has the capacity to induce enzymes from the CYP 3A4 sub family. The study was designed to investigate the possible influence of single (600 mg) and repeated doses of OXC (400 mg bid) on the steady state pharmacokinetics of felodipine (10 mg qd for 13 days) in healthy volunteers. The pharmacokinetics of felodipine and its pyridine metabolite following administration of felodipine alone were similar to those following coadministration with a single 600 mg dose of OXC. Following repeated administration of OXC (450 mg bid), the mean exposure and Cmax for felodipine were 28% and 34% lower, respectively, compared to that following felodipine alone. However, the plasma concentrations of felodipine were still in the recommended therapeutic range. Similar results were obtained for the pyridine metabolite of felodipine. No change in its pharmacokinetic parameters were observed after coadministration with a single dose of OXC. However, after coadministration with repeated doses of OXC, the mean exposure and Cmax were lowered by 37% and 35%, respectively. Since coadministration with OXC did not increase the exposure to the pyridine metabolite of felodipine, the metabolic processes involved in the oxidation of felodipine to the pyridine metabolite are probably not affected by OXC. The reduction in the felodipine exposure by 28% due to concomitant administration with OXC may be due to the influence of OXC on other metabolic pathways of felodipine. The bioavailability of felodipine and its metabolite is decreased following coadministration with OXC. However, since felodipine concentrations were still in the therapeutic range, no dosage changes for felodipine have been recommended.

Effect of single and repeated doses of OXC on the Pharmacodynamics of Warfarin: The objective of this study was to investigate the pharmacodynamic effect of Coumadin (sodium warfarin) under steady state conditions, before and after treatment with single (600 mg) and multiple doses (450 mg bid) of OXC. During warfarin titration phase, the warfarin dose was titrated to achieve a Quick Time (measure of prothrombin time) of 35-45%. During the warfarin maintenance phase, the warfarin dose was maintained at the level established during the titration phase. Because the Quick times were found not to be reaching the target range of 35-45% in most subjects during the planned warfarin titration phase, this period was extended to day 20.

1 page
REDACTED
DRAFT
LABELING

PRECAUTIONS
Drug Interactions

Antiepileptic drugs

- For Table 3A: **Summary of AED Interactions**: Please indicate clearly in the label whether the changes observed are changes in AUC or Cmin. Also please include in each case, a measure of variability, such as 90% confidence interval. The following format for the table (3A) is recommended.

Coadministered AED	Dose of AED	OXC Dose	N	Coadministered AED (% Change)		MHD (% Change)	
				AUC mean (90%CI)	Cmin mean (90%CI)	AUC mean (90%CI)	Cmin mean (90%CI)

Hormonal Contraceptives

- Please include in a measure of variability, such as a 90% confidence interval along with the mean change in AUC of the coadministered drug(s).

Calcium Antagonists

- Please include in a measure of variability, such as a 90% confidence interval along with the mean change in AUC of the coadministered drug(s). The following format for an additional table (3B: **Summary of interactions with other drugs**) is recommended.

Coadministered AED	Dose of Coadministered drug	OXC Dose	N	Coadministered Drug(% Change)		MHD (% Change)	
				AUC mean (90%CI)	Cmin mean (90%CI)	AUC mean (90%CI)	Cmin mean (90%CI)

/S/

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drugs Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Concurrence: Chandra Sahajwalla, Ph.D.
Team Leader, Neuropharmacological Drugs Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics
cc: HFD-120 NDA 21014
/MO/N. Hershkowitz
/CSO/M. Malandrucco
/Biopharm/V.Sekar
/TL Biopharm/C. Sahajwalla
HFD-340 /Viswanathan
HFD-860 /DPE1
CDR Document Room