CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20646

BIOEQUIVALENCE REVIEW(S)

Tiagabine HCl
4, 12, 16 and 20 mg tablets
NDA 20-646
Reviewer: Iftekhar Mahmood, Ph. D.
Submission Date: March 31, 1997.
Indication: Antiepileptic

Abbott Laboratories
Pharmaceutical Products Division
Abbott Park, Illinois 60064

Based upon the solubility characteristics of tiagabine (24 mg/mL), the Sponsor proposed the following Dissolution Method and Specifications for tiagabine tablets:

Strengths:
Apparatus:
Medium:
Speed:

Sponsor's proposed Specifications: Q = at 30 minutes.
FDA's proposed Specifications: Q = at 30 minutes.

Upon reviewing the proposed dissolution specification, the FDA requested that the Sponsor should use instead of in order to mimic physiological conditions. In response, the Sponsor has provided dissolution profiles in which is similar to dissolution profiles in water.

Recommendation:

Due to the similarity in dissolution profiles in the dissolution method for tiagabine as proposed by the Sponsor (using as medium) is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Iftekhar Mahmood 9/4/97
Iftekhar Mahmood, Ph. D.
Division of Pharmaceutical Evaluation I

FT initialed by Raman Baweja, Ph. D. R. Baweja 9/4/97.

CC: NDA 20-646
HFD-120, HFD-860 (Mahmood, Baweja, Malinowski), CDR (Barbara Murphy for Drug Files).

Tiagabine HCl
4, 12, 16 and 20 mg tablets
NDA 20-646
Reviewer: Iftekhar Mahmood, Ph. D.
Submission Date: March 31, 1997.
Indication: Antiepileptic

Abbott Laboratories
Pharmaceutical Products Division
Abbott Park, Illinois 60064

Study #1

Title: The bioavailability of a 20 mg tiagabine HCl tablet relative to a reference 4 mg tablet under fasting conditions (M96-546 (TIA-091).

Abbott Laboratories have submitted the results of the above mentioned bioequivalence study. Earlier in their NDA submission (20-649), the Sponsor tried to demonstrate bioequivalence between a reference 4 mg tablet (to which all the bioequivalence/clinical studies were linked) and the proposed commercial 20 mg tablet formulation (highest strength). The study failed to demonstrate bioequivalence as the 90% confidence interval for C_{max} (99-133%) was outside the acceptable interval of 80-125%. This study was conducted as a multiple dose in the fed state in patients with epilepsy who were on existing antiepileptic drugs (phenytoin, carbamazepine and valproic acid). Food, multiple dose and perturbation of enzymatic activity may have contributed to both intra- and inter-individual variation to the extent where C_{max} failed to meet the 90% confidence interval criteria. The 18% higher C_{max} observed with the 20 mg tablet raised concern about the safety of this highest tablet strength and the information submitted to establish the safety of the 20 mg tablet was not convincing to the Clinical Division. Therefore, Abbott Laboratories decided to conduct a definitive bioequivalence study (1x20 mg vs 5x4 mg tablets) in 60 patients with epilepsy taking one or two enzyme-inducing antiepilepsy drugs. This was a single dose, fasting, open-label, two-period, crossover study. The results of this study indicate that the two formulations (1x20 mg tablet and 5x4 mg tablets) are bioequivalent.

Comments to OCPB

1. This study indicates that sample size can play an important role in bioequivalence studies. The selection of the number of subjects in this study was based upon the statistical calulation which indicated that the probability (power) of meeting the

bioequivalence criteria for C_{max} would be 98% if 56 subjects are included in the study. Thus, sixty subjects were included in the study to compensate for drop outs.

2. This study is a single dose study and the Sponsor was advised to conduct a single dose study by OCPB immediately after the submission of their NDA.

3. In the previous study the highest observed C_{max} was 507 ng/mL. In this study, the highest C_{max} was 964 ng/mL and the subject completed the study. Two female volunteers dropped out from the study. One volunteer had a C_{max} of 190 ng/mL whereas no sample could be taken from another volunteer.

Study #2

Title: Dissolution profiles of tiagabine

Comment to the Sponsor

4. Since the dissolution profiles at physiological pH range are more relevant, the following **"interim"** Dissolution Method and Specification for tiagabine tablets is proposed by the **FDA.**

Strengths: 4, 12, 16 and 20 mg tablets
Apparatus:
Medium:
Speed:
Sampling Times:

FDA's proposed Specifications: Not Less Than at 30 minutes.

The Sponsor should test production lots using the FDA recommended"interim" dissolution specification and method, and also the dissolution method and specification proposed by the Sponsor (which was used to support the stability studies in this NDA) during their post-approval stability studies. Based upon the results of these tests, and following expiration of the current expiry date, the **"interim"** dissolution specification

should then be adopted as the final dissolution method and specification for all strengths of tiagabine tablets.

Recommendation:

The 20 mg to-be-marketed tablet has been shown to be bioequivalent to the 4 mg to-be-marketed tablet.

Please convey Comment 4 and the Recommendation to the Sponsor.

Iftekhar Mahmood, Ph.D. 6/23/97

FT initialed by Mohammad Hossain, Ph.D. 6/23/97

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA 20-646
HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), CDR (Barbara Murphy)

JUL 1 2 1996

Tibex™ (tiagabine HCl)
4, 12, 16, and 20 mg tablets
NDA 20-646 (NME)

Abbott Laboratories
Abbott Park, IL 60064.
Submission Dates: November 3, 1995
May 16, 1996.

DETIRN
JUL 1 3 1996

Reviewer: Iftekhar Mahmood, Ph. D.

INTRODUCTION

TIBEX (tiagabine HCl) is an antiepileptic drug. Its chemical name is (R)-(-)-1-[4, 4-Bis (3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid hydrochloride. Its molecular weight is 412. It is insoluble in heptane, very soluble in water (24 mg/mL), and soluble in aqueous base (3 mg/mL). Tiagabine is a potent and selective inhibitor of gamma-aminobutyric acid (GABA) uptake in presynaptic neurons. Abbott and Novo-Nordisk are developing this compound jointly for the treatment of epilepsy.

Enhancement of GABA activity has been shown to inhibit seizures while reduction of GABA activity increases seizures. Tiagabine enhances the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

Following intravenous administration of tiagabine, the mean V_{ss} and V_{area} were approximately 75 ± 15 L and 92 ± 16 L, respectively. These values exceed total body water (40-46 L), suggesting that tiagabine distributes into tissues. Following intravenous administration, the mean total plasma clearance was 109 ± 25 mL/min. The elimination half-life for tiagabine observed in healthy subjects and uninduced (hepatic enzyme) epileptic patients ranges from 7 to 9 hours. The elimination half-life decreased by 50-65% in hepatic enzyme-induced epileptc patients (mean $t_{1/2}$ = 3 hours)

Tiagabine is well absorbed and T_{max} values ranged from 0.25 to 3 hr after oral dosing. The C_{max} values ranged between 10 and 35 ng/mL per mg of tiagabine HCl when administered orally. The mean absolute bioavailability of tiagabine was 90%.

Administration of tiagabine HCl tablets with a high fat breakfast decreased the rate but not the extent of tiagabine absorption. Mean values of C_{max} and AUC increased with dose, demonstrating dose proportionality over the single dose range of 2-24 mg.

Tiagabine is extensively metabolized, and at least two metabolic pathways for tiagabine in humans have been identified, 1) thiophene ring oxidation involving CYP 3A isozyme; and 2) glucuronidation. Tiagabine is highly bound to plasma proteins (96%) in humans over the therapeutic concentration range.

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The Sponsor submitted 63 studies of which 36 were reviewed. Out of 10 bioequivalence studies, 3 studies were reviewed since these were pivotal studies. Eleven studies were not reviewed because these were pre-clinical studies, whereas 5 studies were clinically oriented of which 2 were reviewed. The analytical methods were presented in 3 studies, which were summarized as one study in this review. Six studies were considered irrelevant as they have no impact on this NDA.

NOTE: The appendices contain more detailed data/information on individual study summary as mentioned in Table of Contents. This information is being retained in the Office of Clinical Pharmacology and Biopharmaceutics, and can be obtained upon request.

SUMMARY

Pharmacokinetics:

Bioequivalence:

The tiagabine HCl dosage form planned for marketing in the United States is a tablet (Formula G) manufactured by Abbott Laboratories (Abbott Park, Ill) of 4, 12, 16 and 20 mg strengths. All four tablet strengths are manufactured from the same formulation (i.e., the drug/excipient ratios are the same for all strengths) and the tablets differ only in weight. The 4 mg clinical tablet (Formula B-4, North Chicago, Ill) used in the clinical studies (M91-605 & M91-603) was found to be bioequivalent to 4 mg market tablet (G-4) (Study #4). However, the 4 mg clinical tablet (B-4) was bioinequivalent to the 20 mg market tablet (G-20). The 90% confidence interval for AUC (0-12), C_{max} and C_{min} ranged from 0.993-1.112, 0.992-1.332, 0.968-1.260, respectively (Study #3).

The multiple dose bioequivalence (BE) study (Protocol M94-156) shows that the test 1x20 mg tablet of tiagabine HCl planned for marketing is equivalent to the clinically-tested 5x4-mg reference tablet with respect to the extent of absorption (AUC_{0-12}). The confidence interval for C_{max} does not meet the requirements to demonstrate bioequivalence. The C_{max} tends to be higher and may be somewhat more variable for one 20 mg tablet (CV= 47%) than for five 4-mg tablets (CV = 30%). Both formulations were given with food (food decreases C_{max} and prolongs T_{max}, but AUC remains unchanged). The 18% higher C_{max} with one 20 mg tablet (218.4 ± 103.3 ng/mL vs 183.3 ± 53.4 ng/mL) may not be of safety concern, since in this study there were subjects whose C_{max} value was > 300 ng/mL and these subjects completed the study without any adverse effect. Furthermore, tiagabine doses will be titrated to epileptic patients. It should be noted that clinically higher doses of 64 to 80 mg/day have been administered; however, the highest dose proposed in the labeling is only 56 mg/day (based on efficacy).

In a second single dose BE study (Study #4; Protocol M94-157), 2x4 mg tiagabine tablets (test, planned for marketing) when given to healthy volunteers under fasting state were found to be bioequivalent to 2x4 mg tablets (reference) used in the pivotal clinical trial for both AUC and C_{max}. In the same study, 2x4 mg tablets (test) was given with food. Food decreased the C_{max} and increased the T_{max} but AUC remained unchanged.

For this NDA the sponsor has conducted a total of 10 bioequivalency studies; only the multiple dose BE study (n=22 patients) conducted in the fed state fails for C_{max}. The

remaining 9 BE studies conducted as a single dose, fasting study involving 18-30 healthy subjects easily passed 90% C.I. for both C_{max} and AUC, which is supported by the fact that tiagabine is a highly soluble (1-24 mg/mL over the physiological pH range; dose/solubility volume <<250 mL), highly permeable (F_{abs}>90% and <2% excreted as unchanged drug). The sponsor was also able to demonstrate that under fasting state the 4 mg (to-be-market tablet) is bioequivalent to the 4 mg (clinical) tablet based on both C_{max} and AUC. In 5 out of 9 single dose BE studies, the 4 mg clinical tablet was shown to be bioequivalent (C_{max} and AUC) to a wide variety of formulations and given as high as 8 multiple units of a tablet strength (i.e., 8 x 1mg tablet). The two food studies conducted, consistently showed a decrease in the rate of absorption but not the extent. Evidently, the multiple dose BE study (where C_{max} fails but AUC passes) was conducted in the fed state and in patients who were also recieving hepatic enzyme-inducing antiepileptic drugs. Perturbation of enzyme activity may also contribute to both intra- and inter-individual variation with respect to the metabolism of this drug.

Biowaiver:

Based upon the 2 bioequivalence studies (Studies 3 &4), the Sponsor is seeking biowaiver for the 12 and 16 mg to be marketed tiagabine tablets. The 4, 12, 16, and 20 mg tablets are compositionally proportional. The dissolution profiles of all four strengths of tiagabine HCl in water, 0.05M phosphate buffer (pH = 7.5) ar.d 0.1N HCl indicated that the release profiles were similar in all three media for all four strengths (by 30 minutes the release was more than 85%).

The two tablet strengths and formulations (1x 20 mg test tablet or 5x4 mg reference tablets) may not be bioequivalent but taking into consideration the safety, dose titration, adjunct therapy, the linear pharmacokinetics of tiagabine, the comparable multi-media dissolution profiles and the compositional proportionality of 4, 12, 16 and 20 mg tiagabine tablets, a waiver request for bioequivalence studies for 12 and 16 mg tiagabine tablets may be granted and an additional bioequivalence study for the 20 mg to be marketed tablet may not be necessary.

The labeling proposed by Abbott indicates that tiagabine doses will be titrated in epileptic patients (starting at 4-8 mg/day to a maximum of 32-56 mg/day, given in divided doses 2-4 times daily). It is important to note that sponsor proposes that doses may be increased by 8-12 mg at weekly intervals), and therefore, will not involve the highest strength tablets of tiagabine. Also, because of dose titration to a clinical response, the sponsor states that any observed adverse events are usually treated either with no change in dose or a dose reduction, with only a few percent cases where tiagabine had to be discontinued.

Taking into consideration all of the above information, the Office of Clinical Pharmacology and Biopharmaceutics would grant the sponsor waiver of bio-studies for the 12 mg and 16 mg to-be-market tablets. From a biopharmaceutic standpoint, the 20 mg to-be-market tablet should also be approved (it is equivalent for AUC) unless there is a safety concern for the 20% higher C_{max} based on the Clinical Division's review of safety data generated using this to-be-market tablet strength and/or the absence of safety data at higher than the maximum proposed labeling dose of 56 mg/day. Appropriate labeling information can be provided as necessary to address the higher C_{max} observed with the 20 mg market image tablet.

Absorption, distribution, metabolism and elimination:

The mean absolute bioavailability of tiagabine was 90% when an oral tablet was compared to an intravenous infusion (Study #4a). The extent of absorption of tiagabine from solid oral dosage forms (tablets & capsules) was 94% to that from an oral solution (Study #1).

Tiagabine is rapidly absorbed when administered orally under fasting conditions to healthy subjects. T_{max} values ranged from 0.25 to 3 hr after dosing. C_{max} values ranged between 10 and 35 ng/mL per mg of tiagabine HCl when administered orally.

Following intravenous administration of tiagabine, the mean V_{ss} and V_{area} were approximately 75 ± 15 L and 92 ± 17 L respectively, for a 70 kg individual. These values exceed common estimates of total body water (40-46 L), suggesting that tiagabine distributes into tissues.

Following administration of a single 4 mg dose of ^{14}C-tiagabine HCl to healthy subjects, unchanged tiagabine accounted for most (70-80%) of the circulating radioactivity in plasma. Approximately 25% of the radioactivity was excreted in the urine, primarily during the initial 36 hours. The remaining radioactivity was slowly eliminated in the feces (mean = 63%; range = 45-75%), largely within 3-5 days after dosing. The total recoveries of the ^{14}C-dose averaged 88% but were ≥95% in three of the four subjects. Tiagabine was extensively metabolized, as evidenced by the excretion of only 2% of the ^{14}C-dose as the unchanged parent drug (Study #5).

At least two metabolic pathways for tiagabine in humans have been identified, based on *in vivo* and *in vitro* studies: 1) thiophene ring oxidation leading to the formation of 5-oxo-tiagabine; and 2) glucuronidation. However, the metabolism of tiagabine in humans has only been partially elucidated, and in particular, two major metabolites in human feces could not be identified, due to the apparent instability of these

metabolites and the low dose of tiagabine (4 mg) that was administered to the subjects (Study #5).

In vitro studies suggest that the principal isoform(s) responsible for the metabolism of tiagabine belongs primarily to the CYP3A subfamily. The disappearance of tiagabine and formation of the inactive metabolite 5-oxo tiagabine were inhibited by the following CYP3A selective inhibitors: 50 μM clotrimazole (≥ 90% inhibition at 50 μM tiagabine), 2 μM ketoconazole (39-50% inhibition at 50 μM tiagabine; 44-60% inhibition at 500 μM tiagabine), 100 μM troleandomycin (49-59% inhibition at 50 μM), and 200 μM erythromycin A (43-52% inhibition at 50 μM). Although contributions from CYP1A2, CYP2D6 or CYP 2C19 could not be excluded in tiagabine metabolism.

The effect of tiagabine on the CYP3A mediated metabolism of terfenadine (20 μM) in human liver microsomes was studied in an attempt to predict the potential for an *in vivo* interaction between the two drugs. The results indicated that tiagabine, at concentrations up to 200 μM, did not inhibit (≤11%) the metabolism of terfenadine. Since the estimated concentration of unbound tiagabine in the liver is only 0.2 μM, these *in vitro* results suggested that tiagabine would not affect the oxidative metabolism of terfenadine *in vivo*.

Tiagabine is highly bound to plasma proteins in humans. The *in vitro* protein binding of [^{14}C]tiagabine in human plasma was independent of concentration over a 0.01 to 10 μg/mL range, which was similar in males and females, and averaged 96%. Tiagabine is bound to both human serum albumin (89%) and α_1-acid glycoprotein (69%), but albumin appears to be the more important binding protein. *In vitro* studies demonstrated that the distribution of tiagabine in human blood favored the extracellular fraction, with a mean blood/plasma concentration ratio of 0.65, a red blood cell/plasma concentration ratio of 0.15 and a fraction bound to the blood cells of 0.09.

Following intravenous administration, the mean total plasma clearance was 109 ± 25 mL/min. Total blood clearance was estimated to be 168 mL/min. The blood clearance estimate is a relatively small fraction of total liver blood flow (approximately 11% of 1500 mL/min), indicating that tiagabine is a low extraction ratio drug and that tiagabine clearance should be largely independent of changes in liver blood flow. The elimination half-life for tiagabine observed in healthy subjects ranged from 7 to 9 hours (Study #4a). The elimination half-life decreased by 50-65% in hepatic enzyme-induced epileptic patients (3 hours) as compared to uninduced epileptic patients (8 hours).

Food Effect:

Administration of tiagabine HCl tablets with a high fat breakfast (three scrambled eggs with one pat of butter and 30 mL cream, three slices of wholegrain toast with two

pats of butter and 300 mL whole milk; total fat content of the breakfast was approximately 73 g) decreased the rate of absorption of tiagabine but not the extent. The mean T_{max} increased from 0.7 to 2.5 hours, and the mean C_{max} decreased from 164 to 92 ng/mL (by 45%) when the tablet was administered with food (Study #4).

Dose Proportionality:

Mean values of C_{max} and AUC of tiagabine increased with dose, demonstrating dose proportionality over the single dose range of 2-24 mg (Study #6).

Multiple Dosing:

Negligible accumulation was observed when tiagabine HCl is administered once daily (Study #7). The steady state C_{max} value following 4 mg oral dose given once daily was 86 ng/mL (CV = 42%). Steady state is achieved within 2 days following oral administration of tiagabine. Based upon an average half-life of 8 hours, following multiple dosing given as BID, TID, and QID regimen the expected accumulation of tiagabine will be 1.5, 2 and 2.5 fold, respectively.

Hepatic Impairment:

Subjects with mild or moderate impairment of liver function had higher plasma concentrations of both total and unbound tiagabine than normal healthy subjects. The protein binding of tiagabine was decreased in subjects with moderate hepatic impairment and clearance of unbound tiagabine was reduced by 60%. Tiagabine HCl doses should be carefully titrated in epileptic patients with reduced hepatic function. Lower tiagabine HCl doses or longer dosing intervals may be necessary (Study #9).

Renal Impairment:

The pharmacokinetics of total and unbound tiagabine were similar in subjects with normal renal function and in subjects with mild, moderate or severe renal impairment. The pharmacokinetics of total and unbound tiagabine was also unaffected in subjects with renal failure requiring hemodialysis (Study #10).

Age:

The pharmacokinetic profile of tiagabine was not significantly different between healthy elderly subjects and healthy young subjects. Regression analyses on data from children and adults showed a strong relationship between body size (weight or surface area) and clearance. When tiagabine clearance and volume of distribution were determined per kg of body weight, children (3-10 years) tended to have somewhat higher values than adults. When determined per m^2 of body surface area, clearance and volume of distribution values in adults and children were generally similar in the induced group.

These observations are consistent with previous data from adults with epilepsy. However, in uninduced epileptic children clearance based upon body weight and body surface area was 2 and 1.5-fold higher, respectively, compared to uninduced epileptic adults (Studies #11 & 12).

Gender:

There is no difference in the pharmacokinetics of tiagabine due to gender in healthy and epileptic patients when adjusted for body weight (Studies #4 & 25).

Chronopharmacokinetics:

A diurnal effect on the pharmacokinetics of tiagabine was observed. In a multiple dose study (Study #10), mean steady-state C_{min} PM values were lower by 40% than mean C_{min} AM values. A similar observation was noted when tiagabine steady-state AUC values were found to be lower by 15%, following the evening tiagabine HCl dose than the morning dose (Study #13).

Drug-Drug Interactions:

Numerous studies examined the potential for *in vivo* pharmacokinetic drug interactions between tiagabine and a variety of other drugs including, carbamazepine, phenytoin, valproate, oral contraceptives, warfarin, theophylline, digoxin, triazolam, ethanol, and cimetidine (Studies #13-24). The results of these studies indicate that there was a relatively small (on an average 10-12%) decrease in the mean C_{max} and AUC_{0-t} values for valproic acid when administered with tiagabine HCl. This decrease may not be of any clinical significance. It should be noted that valproic acid decreased tiagabine protein binding, which resulted in 40% increase in free tiagabine concentration in-vitro. A small (about 5%) increase in tiagabine AUC was observed when tiagabine HCl was administered with cimetidine, which also may not be of any clinical significance. No statistically ($p < 0.05$) significant differences in the pharmacokinetics of oral

contraceptives, warfarin, theophylline, digoxin, triazolam, phenytoin, carbamazepine and ethanol were observed when given with tiagabine. The only drug interactions with clear clinical importance are those between tiagabine and the enzyme-inducing antiepileptic drugs, e.g., carbamazepine and phenytoin. Limited pharmacokinetic data suggest that phenobarbital, primidone and vigabatrin may also induce the metabolism of tiagabine. The clearance of tiagabine is 2 to 4 times greater, on average, in epileptic patients taking enzyme inducing antiepileptic drugs suggesting that induced patients may require larger and/or more frequent doses of tiagabine HCl than uninduced patients.

Oral clearance and half-life values for antipyrine were not significantly different before and after tiagabine doses upto 12 mg/day for 14 days. Tiagabine does not appear to cause induction or inhibition of the hepatic microsomal enzyme systems responsible for the metabolism of antipyrine (Study #8).

Population pharmacokinetics:

From the population pharmacokinetic analyses, the most important covariate of tiagabine clearance was found to be coadministration of AEDs known to induce hepatic drug metabolism (e.g. carbamazepine, phenytoin and barbiturates). The CL/F estimate in induced patients was 21.4 L/h and was 67% higher than the value for the noninduced patients (12.8 L/h). CL/F estimates were found to be positively correlated with body weight and negatively with plasma albumin concentrations, but the correlations only explained a small fraction of the interpatient variability in CL/F. No other demographic variables, including age, race and smoking, or any clinical chemistry measurements, including bilirubin, SGOT, and SGPT, were of importance in explaining the variability in the CL/F estimates (Study #25).

It should be noted that the NONMEM analysis was found to be inadequately conducted (i.e. exclusion of outliers without scientific justifications; absence of intercept in the pharmacostatistical model, multiexponential models were not tested; a significant amount of residual variability, 67%, still remained unexplained). The predictive performance of the final population model (i.e. model validation) has not been performed.

Pharmacodynamics:

The effect of orally administered tiagabine HCl on extracellular GABA concentrations in the hippocampi of patients with complex partial seizures was evaluated in seven patients receiving a single dose of 16 mg tiagabine HCl, 2 patients receiving a single dose of 24 mg tiagabine HCl and 3 patients receiving two doses of tiagabine HCl

administered as 12 mg BID. Bilateral intracranial depth electrodes, each modified to include microdialysis probes, were implanted into the hippocampi of each patient. Location of the depth electrodes was verified by magnetic resonance imaging (MRI) of the brain the day after implantation. Tiagabine HCl was administered in the fasting condition. Ten patients completed the study (2 patients receiving 12 mg BID discontinued the study due to adverse effects). The dialysate aliquots were assayed for GABA, while plasma samples obtained at different intervals were analyzed for tiagabine plasma concentrations. The results demonstrated that tiagabine increased GABA concentration in the brain of epileptic patients. The mean increase in GABA concentration of 9.263 nM, represented a statistically significant ($p = 0.005$) increase from the baseline level. No statistically significant ($p = 0.68$) correlation was found between the average change from baseline GABA values and the plasma tiagabine AUC values (Study #26).

Dissolution:

The following are the Sponsor's dissolution method and proposed specifications for all strengths of tiagabine HCl tablets.

Apparatus:
Agitation:
Medium:
Profile Times:
Assay:
Specification:

Based upon data provided by the Sponsor, the Office of Clinical Pharmacology and Biopharmaceutics recommends the following dissolution method and specifications:

Apparatus:
Agitation:
Medium:
Profile Times:
Assay:
Specification:

Comments to the Medical Reviewer

1. Half-life:

The elimination half-life decreased by 50-65% in hepatic enzyme-induced epileptic patients (3 hours) as compared to uninduced epileptic patients (8 hours). Therefore, the hepatic enzyme-induced epileptic patients may require adjustment in their tiagabine dose, with larger and/or more frequent doses of tiagabine.

2. Hepatic Impairment:

Subjects with mild or moderate impairment of liver function had higher plasma concentrations of both total and unbound tiagabine than normal healthy subjects. The protein binding of tiagabine was decreased in subjects with moderate hepatic impairment and clearance of unbound tiagabine is reduced by about 60% and that subjects with reduced serum protein concentrations would have elevated fractions of unbound drug. Tiagabine HCl doses should be carefully titrated in epileptic patients with reduced hepatic function. Lower tiagabine HCl doses or longer dosing intervals may be necessary.

3. Pediatric:

Tiagabine has not been investigated in adequate and well-controlled clinical trials in patients below the age of 12. Currently, the sponsor has only indicated that tiagabine should be used in patients 12 years or older. However, pharmacokinetic information is available in pediatrics upto 3 years of age, which may allow to suggest a pediatric dosing recommendation for this age group provided the course of the disease and the effects of the drug are deemed sufficiently similar to adults. Dosing recommendation in pediatric patients (3-10 yrs old) should be based on body weight or body surface area. The apparent clearance and volume of distribution of tiagabine per unit body surface area or per kg are fairly similar in children (age: 3-10 years) and in adults taking enzyme inducing antiepileptic drugs (e.g. CBZ or phenytoin). Therefore, no dosage adjustment will be necessary in this situation. However, in children who were taking non-inducing AED (e.g. valproate), the clearance of tiagabine based upon body weight and body surface area was 2 and 1.5-fold higher, respectively, compared to uninduced epileptic adults. Therefore, these pediatric patients may require a larger or more frequent doses of tiagabine.

4. Food Effect:

The labelling section of "Dosage and Administration" suggests that tiagabine should be given with food. Most of the pharmacokinetic studies have been conducted under the fed condition. Food effects the rate of tiagabine absorption but not the extent. Therefore, tiagabine should be given on an empty stomach (preferably at least an hour before or two hours after a meal) to avoid a food related decrease in the rate of absorption of tiagabine.

Comments to the Sponsor

1. Bioequivalence and Biowaiver:

The two tablet strengths and formulations (1x 20 mg market tablet or 5x4 mg clinical tablets) may not be bioequivalent but taking into consideration high solubility, high permeability, being a non-highly variable drug, dose titration (starting at 4-8 mg/day to a maximum of 32-56 mg/day, given in divided doses 2-4 times daily, with doses increase by 8 to 12 mg at weekly intervals), the linear pharmacokinetics of tiagabine, the comparable multi-media dissolution profiles and the compositional proportionality of 4, 12, 16 and 20 mg tiagabine tablets, a waiver request for bioequivalence studies for 12 and 16 mg tiagabine tablets is granted to the Sponsor.

2. Dissolution:

The Office of Clinical Pharmacology and Biopharmaceutics recommends the following dissolution method and specifications:

Apparatus:
Agitation:
Medium:
Profile Times:
Assay:
Specification:

3. Metabolism:

The Sponsor is requested to pursue further in-vitro work on CYP2C19.

4. Drug-Interaction Studies:

Ideally, drug-interaction studies should be designed in such a way that the pharmacokinetic parameters can be estimated for both drugs in the presence and absence of each other under steady-state conditions. In this NDA there were studies where plasma samples of tiagabine were not collected long enough to address the effect of other drugs on the pharmacokinetics of tiagabine.

5. Population Analysis:

The NONMEM analysis was found to be inadequately conducted (i.e. exclusion of outliers without scientific justifications; absence of intercept in the pharmacostatistical model; multiexponential models were not tested; a significant amount of residual variability, 67%, still remained unexplained). The predictive performance of the final population model (i.e. model validation) has not been performed. When conducting population PK/PD analysis, the Sponsor is encouraged to submit such protocols for review and input from the Office of Clinical Pharmacology and Biopharmaceutics.

5 pages
purged

Draft Labeling

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the labeling changes.

- Please forward Comments 1-5 and Labeling Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. 7/12/96

FT initialed by Mohammad Hossain, Ph.D. 7/12/96

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

First draft prepared on April 18, 1996.
RD initialed by Mohammad Hossain, Ph.D. on May 8, 1996.
Second draft prepared on June 7, 1996.
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Biopharm Day: June 24, 1996.

CC: NDA 20-646, HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), HFD-870 (Chen Me), HFD-880 (Fleischer), HFD-340 (Viswanathan), and HFD 870: Chron, Drug, Reviewer and FOI (HFD-19) files (Clarence Bott, PKLN, RM 13B-31).

Note: Dr. Mohammad Hossain, Ph.D. assisted in the review and provided the comments involving NONMEM analysis.