CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-710

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: [ ] (Carbamazepine ER) **PRIMARY REVIEWER: Andre Jackson**

NDA: 21710 TYPE: NDA

FORMULATION: ER Capsule STRENGTH: 100 mg, 200 mg and 300 mg

APPLICANT: Shire Submission Date: February 13, 2004
May 10, 2004

INDICATIONS: Epilepsy and Bipolar Disorder

Generic Name: Carbamazepine ER capsules

EXECUTIVE SUMMARY

A clinical study has been conducted by the sponsor for a new indication for carbamazepine, bipolar disorder, for which the sponsor is also seeking to have an alternative name of [ ] for the product. This NDA review evaluates changes to the labeling regarding the potential for drug interactions with carbamazepine(CBZ), as provided by the Sponsor, for all [ ] products. The Sponsor has provided literature references to support the labeling changes, and reference is also made to current labels for specific drugs that refer to these interactions. [ ] (carbamazepine ER capsules) will be prescribed only for BIPOLAR DISORDER. The firm is currently in negotiations with the FDA to determine if they will have two trademark names (ie Carbatrol and [ ] for the two different indications.

Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends that the proposed labeling changes regarding drug interactions are acceptable with the following changes.
1)The drug interactions for:

> zonisamide (remove from P450 inhibitors and move to AGENTS WITH DECREASED LEVELS IN THE PRESENCE OF CBZ.);
>
> methsuximide (added to AGENTS THAT INDUCE P-450).

2) Co-administration of carbamazepine (CBZ) with nefazodone should be CONTRA-INDICATED in the label to be consistent with the current nefazadone label.

3) Delavirdine which shows a loss of virologic response when co-administered with CBZ has been added to AGENTS WITH DECREASED LEVELS in the presence of CBZ and also to the WARNINGS sections of the label.

4) Based upon the current Tegretol label the following compounds were added to AGENTS WITH DECREASED LEVELS in the presence of CBZ (i.e., felodipine, itraconazole, levothyroxine, methadone, oxcarbazepine, praziquantel, tramadol, ziprasidone)

5) It will be helpful to include a statement in "Information for Patients" stating the potential for [ ] to interact with other drugs.

6) The evidence for the interaction with trazodone is based upon a single case report. The sponsor should supply any available additional data to support the inclusion of this interaction in the label.

7) [ ] was removed from the label since it is not currently on the US market.

8) Sertaline was removed from AGENTS THAT INHIBIT P450 since it is unlikely to have a clinical impact on CYP3A4.

9) The current label's reference to Indinavir, Saquinavir and Ritonavir has been generalized to be inclusive of all protease inhibitors.

10) The current label refers to miconazole as an agent that inhibits CBZ metabolism. This has been generalized to include all azole antifungals.

The changes recommended by OCPB to the proposed label's text can be found on pages 3-6 of this review.

PLEASE FORWARD THE LABELING COMMENTS TO THE SPONSOR.

When the labeling changes become final, OCPB will forward them to the appropriate Divisions of OCPB for inclusion in the labeling of the interacting drugs.

OCPB recommends that a biowaiver be granted for the *in vivo* bioavailability study.

COMMENTS TO THE MEDICAL OFFICER/PROJECT MANAGER

Remacemide is an IND [ ] and is currently inactive as of 2/11/02. Therefore, it should not be included in the list of drugs that may increase [ ] levels.

Zonisamide was removed from P450 inhibitors and moved to AGENTS WITH DECREASED LEVELS in presence of CBZ.

Co-administration of carbamazepine (CBZ) with nefazodone should be CONTRA-INDICATED in the label to be consistent with the current nefazadone label.

Delavirdine which shows a loss of virologic response when co-administered with CBZ has been added to AGENTS WITH DECREASED LEVELS in the presence of CBZ and also to the WARNINGS sections of the label.

Based upon the current Tegretol label the following compounds were added to AGENTS WITH DECREASED LEVELS in the presence of CBZ (i.e., felodipine, itraconazole, levothyroxine, methadone, oxcarbazepine, prizaquantel, tramadol, ziprasidone)

The footnote has been added to drugs known to increase epoxide metabolite levels since toxic effects may appear due to the increased metabolite levels while carbamazepine levels appear normal.

Methsuximide was added to agents that induce CBZ metabolism.

Phensuximide and Methsuximide have similar drug interaction characteristics with CBZ but Phensuximide is currently not on the US market. Therefore, it was deleted from the agents with decreased levels in the presence of CBZ part of the label.

[ ] was removed from the label since it was based upon a single case report.

[ ] was removed from the label since it is not currently on the US market.

Sertaline was removed from AGENTS THAT INHIBIT P450 since it is unlikely to have a clinical impact on CYP3A4.

The current label's reference to Indinavir, Saquinavir and Ritonavir has been generalized to be inclusive of all protease inhibitors

The current label refers to miconazole as an agent that inhibits CBZ metabolism. This has been generalized to include all azole antifungals.

There are discrepancies between the [ ] Carbatrol and Tegretol labels as shown in the Appendix Tables 1 and 2. These differences should be reconciled.

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Background and Overview

Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life ranged from 35-40 hours and 12-17 hours following repeated dosing.

A program of clinical pharmacology studies was presented in the original Carbatrol NDA 20-712. Consequently, this clinical section of the marketing application for carbamazepine extended-release capsules in the acute treatment of manic and mixed episodes in patients with bipolar disorders comprises a cross-reference to NDA 20-712 (volume 1.24, section 8,) and a literature review of the pharmacokinetic and pharmacodynamic information published.

The kinetics have been previously established. Carbamazepine is almost completely cleared by metabolism and the continued presence of the drug produces significant enzyme induction, (Carbatrol NDA 20-712, volume 1.9, page 6).

Current Submission

The firm is proposing to market the [ ] product with a different capsule shell color to distinguish it from Carbatrol. With the exception of the colors in the capsule shells, [ ] (carbamazepine extended release capsules) 100mg, 200mg and 300mg is the same drug product as Carbatrol@ (carbamazepine extended-release capsules) 100mg, 200mg and 300mg respectively. Furthermore, the manufacturing process, manufacturing/testing facilities, analytical methods for release and stability testing, and packaging configurations are identical for both products. The new capsule shell colors for [ ] were achieved by [ ] used in the currently marketed capsule shells for Carbatrol.

Shire is therefore cross-referencing the Carbatrol NDA application (NDA 20-712) which was previously approved by the Agency

Since [ ] is likely to be co-administered with other drugs, Shire has evaluated the potential for drug-drug interactions as part of their development program through published clinical literature review for carbamazepine. Shire believes the literature provides adequate information to assess the drug-drug interaction potential of carbamazepine given that carbamazepine containing drug products have been marketed for over 30 years and the metabolic pathways,

enzymology, therapeutic index and the presence of active metabolites have been completely elucidated.

Therefore, the firm's review of clinical and scientific literature focused on drugs products other then those currently mentioned in the Carbatrol Package insert that are CYP enzymes inhibitors or inducers and whether they are likely to be administered to patients with bipolar disorders or not. The firm has concluded that interactions not yet studied clinically can be predicted rationally from the body of literature already available for carbamazepine.

SUMMARY OF OCPB FINDINGS RELATED TO CYP MEDIATED INTERACTIONS

The Tables in Appendix 1 delineates the differences between the proposed [ ] label and the current Carbatrol and Tegretol labels. Justification for changes to the [ ] label that are consistent with the current Carbatrol and Tegretol labels are presented in Appendix 2.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends that the proposed labeling changes regarding drug interactions are acceptable with the following changes:

DETAILED LABELING RECOMMENDATIONS (only the reviewer changed sections are included here)

OCPB LABEL

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

[ ]

WARNINGS

General

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Co-administration of CBZ and Delavirdine may lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

[ ]

Suicide: The possibility of suicide attempt is inherent in Bipolar Disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for [ ] should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

If necessary, the [ ] capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. [ ] capsules or their contents should not be crushed or chewed.

[ ] may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or non-prescription medication or herbal products.

Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

Agents highly bound to plasma protein:
Carbamazepine is not highly bound to plasma proteins; therefore, administration of [ ] to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that inhibits Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase:
Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of [ ], are the following:

Acetazolamide, azole antifungals, cimetidine, clarithromycin(1), dalfopristin, danazol, delavirdine, diltiazem, erythromycin(1), fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazadone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, [ ] *stiripentol, terfenadine,* [ ] *troleandomycin, valnoctamide(2), valproate(1), valpromide(2) verapamil, zileuton* [ ]

(1)also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11- epoxide

(2) pro-drug of valproic acid also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10,11-epoxide

[ ]

[ ]

Thus, if a patient has been titrated to a stable dosage of [ ], and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for [ ] may be necessary.

Agents that induce Cytochrome P450 Isoenzymes:
Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of [ ] are the following:

Cisplastin, doxorubicin HCL, felbamate, rifampin, phenobarbital, Phenytoin(2), primidone, methsuximide, and theophylline

(2)Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

Thus, if a patient has been titrated to a stable dosage on [ ], and then begins a course of treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for [ ] may be necessary.

Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes

Carbamazepine is known to induce CYP1A2, [ ] and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence of [ ] due to induction of CYP enzymes are the following:

Acetaminophen, alprazolam, amytryptiline, bromperidol, bupropion, buspirone citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, [ ] itraconazole, lamotrigine, levothyroxine, lorazepam [ ] methadone, midazolam, mirtazapine, nortryptilin, olanzapine, oral contraceptives[3], oxcarbazepine [ ] Phenytoin[4], prizaquantel, protease inhibitors, quetiapine, [ ] risperadone, theophylline, topiramate, tiagabine, tramadol, triazolam, valproate, warfarin[5], ziprasidone, and zonisamide.

[3]Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

[4]Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma ——levels following co-medication with carbamazepine is advised.

[5]Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

[ ]

[ ]

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with [ ] it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

Agents ~~with that~~ Increased Levels in the presence of Carbamazepine:

[ ] increases the plasma levels of the following agents:

Clomipramine HCl, Phenytoin[6], and primidone

[6]Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of the treatment with [ ] it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.

[6]Increased levels of the active 10, 11-epoxide

Pharmacological/Pharmacodynamic Interactions with Carbamazepine
Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Given the anticonvulsant properties of carbamazepine, [ ] may reduce the thyroid function as has been reported with other anticonvulsants. Additionally, anti-malarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine.

Thus if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with [ ] it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when [ ] is taken with other centrally acting drugs and alcohol.

IN VITRO DATA

The firm has also supplied dissolution and composition data to compare the new [ ] product to the currently marketed Carbitrol product. The firm's response to an FDA inquiry related to the originally submitted dissolution data is in the Appendix.

The bioequivalence of [ ] (extended-release capsules) 100 mg, 200 mg, and 300 mg can be established by in vitro testing in accordance with 21 CFR 320.22 (d)(2)(i) -(iii). The firm is requesting an in vivo bioavailability waiver for [ ] (extended-release capsules) 100 mg, 200 mg, and 300 mg since they have the same qualitative and quantitative components as Carbatrol@ (extended-release capsules) 100 mg, 200 mg, and 300 mg.

Dissolution profiles generated for [ ] (extended-release capsules) 100 mg, 200 mg, and 300 mg and Carbatrol (extended-release capsules) 100 mg, 200 mg, and 300 mg demonstrate the comparability of the products.

The firm has conducted comparative dissolution profile studies of each strength of [ ] against each strength of Carbatrol using the current approved dissolution procedure for testing Carbatrol. The dissolution profile comparisons resulted in f2 similarity factors of ~ 50.

The f2 comparison (appendix, p.20) of ~ 50 suggest that the dissolution profiles for the 100mg, 200mg and 300mg strengths of [redacted] are correspondingly similar to the dissolution profiles of Carbatrol, 100mg, 200 mg, and 300mg.

The quantitative comparison between the Carbatrol and [redacted] formulations is presented in the following Table.

Base upon the quantitative and qualitative comparisons and the F2 results for the dissolution data, a biowaiver on in vivo data can be granted.

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Quantitative Composition of Carbatrol (100 mg, 200 mg, 300 mg) and SPD417 (100 mg, 200 mg, 300 mg)

Composition of Carbatrol (extended-release capsules) and Intermediate Pellets (%)				
Ingredient	Immediate -Release	Sustained-Release	Enteric-Release	Composite Capsule
Carbamazepine, USP	80.0	69.0	69.0	71.7
Lactose Monohydrate, NF				
Citric Acid, USP (Anhydrous)				
Povidone, USP (K-90)				
Talc, USP				
Microcrystalline Cellulose, NF				
Triethyl Citrate, NF				
Sodium Lauryl Sulfate, NF				
Polyethylene Glycol 400, NF				
Colloidal Silicon Dioxide, NF				
Total	100.0	100.0	100.0	100.0
Percentage of Composite Capsule				

Composition of SPD417 (extended-release capsules) and Intermediate Pellets (%)				
Ingredient	Immediate -Release	Sustained-Release	Enteric-Release	Composite Capsule
Carbamazepine, USP	80.0	69.0	69.0	71.7
Lactose Monohydrate, NF				
Citric Acid, USP (Anhydrous)				
Povidone, USP (K-90)				
Talc, USP				
Microcrystalline Cellulose, NF				
Triethyl Citrate, NF				
Sodium Lauryl Sulfate, NF				
Polyethylene Glycol 400, NF				
Colloidal Silicon Dioxide, NF				
Total	100.0	100.0	100.0	100.0
Percentage of Composite Capsule				

Andre Jackson _____

RD/FT Initialed by Sally Yasuda, Pharm.D._____
Acting Team Leader

Cc NDA 21-710, HFD-120, HFD-860(Jackson, Baweja, Mehta, Rahman,Yasuda), Central Documents Room (Biopharm-CDR)

Path:**C:\Data\REVIEWS\Carbamazepine**] **Shire**

APPENDIX 1

Table 1. Drugs Affected by Induction of P450s by Carbamazepine – ***note***: where [ ] is not consistent with labeling for either Carbatrol or Tegretol, please refer to comments to support rationale for inclusion of the specific drug; does not include drugs that are consistent across all 3 labels			
[ ]	**Carbatrol**	**Tegretol**	**Comments**
Amitriptyline		Amitryptyline	*To PM-include in Carbatrol label*
Bromperidol(1)			To PM –include in Carbatrol and Tegretol labels
Bupropion(2)			To PM –include in Carbatrol and Tegretol labels
Citalopram(3)			To PM –include in Carbatrol and Tegretol labels
Clobazam(4)			To PM –include in Carbatrol and Tegretol labels
Cyclosproine		Cyclosporine	To PM –include in Carbatrol label
Desipramine		(tricyclics)	To PM –include in Carbatrol label
Felodipine		Dihydropyridine calcium channel blockers (e.g. felodipine)	To PM –include in Carbatrol label
Felbamate			To PM –include in Carbatrol and Tegretol labels
Glucocorticoids		Corticosteroids	To PM –include in Carbatrol label
Itraconazole		Itraconazole	To PM –include in Carbatrol label
Protease inhibitors		Protease inhibitors	To PM –include in Carbatrol label
Lamotragine		Lamotrigine	To PM –include in Carbatrol label
Levothyroxine		Levothyroxine	To PM –include in Carbatrol label
Methadone		Methadone	To PM –include in Carbatrol label
Methsuximide		Methsuximide	To PM –include in Carbatrol label
Midazolam		Midazolam	To PM –include in Carbatrol label
Mirtazapine(5)			To PM –include in Carbatrol and Tegretol labels
Nefazodone		Nefazodone	To PM –include in Carbatrol label
Nortiptyline		TCA	To PM –include in Carbatrol label
Olanzapine		Olanzapine	To PM –include in Carbatrol label
Oxcarbazepine		Oxcarbazepine	To PM –include in Carbatrol label
	phensuximide	Phensuximide	To PM-delete from Carbatrol and Tegretol labels
Praziquantel		Praziquantel	To PM –include in Carbatrol label

Quetiapine			To PM –include in Carbatrol and Tegretol labels
Risperidone		Risperidone	To PM –include in Carbatrol label
Topiramate		Topiramate	To PM –include in Carbatrol label
Tiagabine		Tiagabine	To PM –include in Carbatrol label
Triazolam			To PM –include in Carbatrol and Tegretol labels
Tramadol		Tramadol	To PM –include in Carbatrol label
Ziprasidone		Ziprasidone	To PM –include in Carbatrol label
Zonisamide		Zonisamide	To PM –include in Carbatrol label

Table 2. Drugs That Inhibit Metabolism of Carbamazepine – *note*: where [ ] is not consistent with labeling for either Carbatrol or Tegretol, please refer to comments to support rationale for inclusion of the specific drug

[ ]	**Carbatrol**	**Tegretol**	**Comments**
Acetazolamide		Acetazolamde	To PM –include in Carbatrol label
Fluvoxamine(6;7)		Fluvoxamine	To PM –include in Carbatrol label
Nefazodone		Nefazodone	To PM –include in Carbatrol label
Stripentol(8;9)			To PM –include in Carbatrol and Tegretol labels
Delavirdine			To PM –include in Carbatrol and Tegretol labels
Dalfopristine			To PM –include in Carbatrol and Tegretol labels
Grapefruit juice		Grapefruit juice	To PM –include in Carbatrol label
Azole antifungals		Azole antifungals	To PM –include in Carbatrol label
Quinine			To PM –include in Carbatrol and Tegretol labels
Quinupristine			To PM –include in Carbatrol and Tegretol labels
Protease inhibitors		Protease inhibitors	To PM –include in Carbatrol label
Zileuton			To PM –include in Carbatrol and Tegretol labels

APPENDIX 2-SCIENTIFIC EXPLANATIONS

Table 1. Drugs Affected by Induction of P450s by Carbamazepine – *note*: where . [ ] is not consistent with labeling for either Carbatrol or Tegretol, please refer to comments to support rationale for inclusion of the specific drug; does not include drugs that are consistent across all 3 labels

[ ]	**Carbatrol**	**Tegretol**	**Comments**
Amitriptyline		Amitryptyline	
Bromperidol(1)			CBZ 400 mg/day 1-20 weeks decreased bromperidol by 37% and its metabolite by 23%
Bupropion(2)			Cmax and AUC decreased by about 90% after a single dose of bupropion (CBZ at steady state)
Citalopram(3)			CBZ 200-400 mg/day x 4 weeks decreased plasma concentrations of S- and R-citalopram by about 30% in 6 patients
Clobazam(4)			Steady state concentration norclobazam increased 1.4-fold and the ratio of metabolite to parent drug increased 4-fold.
cyclosproine		Cyclosporine	
desipramine		(tricyclics)	
		Dihydropyridine calcium channel blockers (e.g. felodipine)	
Felbamate			Consistent with Felbamate label
Glucocorticoids		Corticosteroids	
		Itraconazole	Consistent with Itraconazole labeling
Protease inhibitors		Protease inhibitors	
lamotragine		Lamotrigine	
		Levothyroxine	Consistent with levothyroxine label
Methsuximide		Methsuximide	
		Methadone	Reviewed in NDA 16-608/SLR 096 for Tegretol; refer to OCPB review
Midazolam		Midazolam	
Mirtazapine(5)			AUC and Cmax for mirtazapine decreased, Cmax for desmethyl increased.
		Nefazodone	Co-administration of carbamazepine with nefazodone is contraindicated, according to SERZONE label due to potential for lack of therapeutic effect.
nortiptyline		TCA	
olanzapine		Olanzapine	
		Oxcarbazepine	Consistent with label for oxcarbazepine
	phensuximide	Phensuximide	
		Priziquantel	Reviewed in NDA 16-608/SLR 096 for Tegretol; refer to OCPB review
Quetiapine			Consistent with label for quetiapine
risperidone		Risperidone	Consistent with label for risperidone
topiramate		Topiramate	
tiagabine		Tiagabine	
Triazolam			Consistent with other benzodiazepines that are CYP3A substrates
		Tramadol	Consistent with label for tramadol
		Ziprasidone	Consistent with label for ziprasidone
		Zonisamide	Consistent with label for zonisamide

Table 2. Drugs That Inhibit Metabolism of Carbamazepine – *note*: where [ ] is not consistent with labeling for either Carbatrol or Tegretol, please refer to comments to support rationale for inclusion of the specific drug			
[ ]	**Carbatrol**	**Tegretol**	**Comments**
Acetazolamide		Acetazolamde	
Fluvoxamine(6;7)		Fluvoxamine	Some evidence for in vivo inhibition of CYP3A by fluvoxamine (using midazolam as probe).
Nefazodone		Nefazodone	
Sertraline			*According to Sertaline label "In three separate in vivo interaction studies, sertraline was co- administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity* ***is not likely to be of clinical significance."***
Stripentol(8;9)			Inhibits CBZ metabolism
Trazodone(10)			Single case report in 1999; no in vitro data or other in vivo data available.
Vigabatrin			Not marketed in US
Zonisamide			***Not consistent with zonisamide label*** *that says "Zonisamide had no appreciable effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidase enzymes (cytochrome P450), as measured in human liver microsomal preparations, in vitro . Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes."*
Delavirdine			*Consistent with label of delavirdine that says "Delavirdine is an inhibitor of CYP3A isoform and other CYP isoforms to a lesser extent including CYP2C9, CYP2D6, and CYP2C19. Coadministration of RESCRIPTOR and drugs primarily metabolized by CYP3A (e.g., HMG-CoA reductase inhibitors, and sildenafil) may result in increased plasma concentrations of the coadministered drug that could increase or prolong both its therapeutic or adverse effects. "*
Dalfopristine			Consistent with Synercid label; Dalfopristin and quinupristin are "Synercid" and according to label inhibits CYP3A
Grapefruit juice		Grapefruit juice	
Azole antifungals		Azole antifungals	Consistent wi th other azole antifungals
Quinine(11)			Supported by literature.
Quinupristine			Consistent with Synercid label; Dalfopristin and quinupristin are "Synercid" and according to label inhibits CYP3A
Protease inhibitors		Protease inhibitors	
Zileuton			Consistent with zileuton label that showed an interaction with terfenadine

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Reference List

(1) Otani K, Ishida M, Yasui N, Kondo T, Mihara K, Suzuki A et al. Interaction between carbamazepine and bromperidol. Eur J Clin Pharmacol 1997; 52(3):219-222.

(2) Ketter TA, Jenkins JB, Schroeder DH, Pazzaglia PJ, Marangell LB, George MS et al. Carbamazepine but not valproate induces bupropion metabolism. J Clin Psychopharmacol 1995; 15(5):327-333.

(3) Steinacher L, Vandel P, Zullino DF, Eap CB, Brawand-Amey M, Baumann P. Carbamazepine augmentation in depressive patients non-responding to citalopram: a pharmacokinetic and clinical pilot study. Eur Neuropsychopharmacol 2002; 12(3):255-260.

(4) Levy RH, Lane EA, Guyot M, Brachet-Liermain A, Cenraud B, Loiseau P. Analysis of parent drug-metabolite relationship in the presence of an inducer. Application to the carbamazepine-clobazam interaction in normal man. Drug Metab Dispos 1983; 11(4):286-292.

(5) Sitsen JM, Maris FA, Timmer CJ. Concomitant use of mirtazapine and cimetidine: a drug-drug interaction study in healthy male subjects. Eur J Clin Pharmacol 2000; 56(5):389-394.

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(8) Cazali N, Tran A, Treluyer JM, Rey E, d'Athis P, Vincent J et al. Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. Br J Clin Pharmacol 2003; 56(5):526-536.

(9) Tran A, Vauzelle-Kervroedan F, Rey E, Pous G, d'Athis P, Chiron C et al. Effect of stiripentol on carbamazepine plasma concentration and metabolism in epileptic children. Eur J Clin Pharmacol 1996; 50(6):497-500.

(10) Romero AS, Delgado RG, Pena MF. Interaction between trazodone and carbamazepine. Ann Pharmacother 1999; 33(12):1370.

(11) Amabeoku GJ, Chikuni O, Akino C, Mutetwa S. Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers. East Afr Med J 1993; 70(2):90-93.

Biopharmaceutics

Your firm has submitted dissolution data for three lots for each strength of [ ] 100mg, 200mg, 300mg (test), and for one lot for each strength of Carbatrol XR (reference). For each strength, and for each time point, you have taken the Grand Mean of the three lots of the test product and compared it to the one reference lot for that strength, and thus obtained the F2 value. Thus, there is one F2 value for each strength for a total of three F2 values in the report.

You are requested to recalculate the F2 values by comparing each individual test lot for each strength to the reference lot for that strength and thus obtaining the F2 values. This implies testing of one test lot to one lot of the reference and thus obtaining the F2 values for each and every lot. This would mean three F2 values for the 100mg strength, three F2 values for the 200mg strength, and three F2 values for the 400mg strength, for a total of nine F2 values. Please note that this Biopharmaceutics information should be provided to the Agency within 2 weeks of receipt of this request letter.

Shire Response:

For clarification, and as per the agreement between Shire and the Agency during the teleconference held on 21 November 2003, Shire performed dissolution profile testing on one (1) lot of each strength of [redacted] (formerly referred to as SPD417) 100mg, 200mg, and 300mg using the current approved dissolution procedure for Carbatrol®. For each strength of [redacted] 12 individual dosage units (N=12) were dissoluted and sampled at the 1, 2, 4, 6, 8, 10, and 12-hour timepoints. The dissolution profile results from the [redacted] batches (test product) were then compared to the Grand Mean of three (3) lots of previously tested Carbatrol® batches (reference product) for each respective strength, using the SUPAC-MR similarity calculation.

Per the agency's request, three individual f2 values were calculated for each strength (100mg, 200mg, and 300mg) for a total of 9 individual f2 values. The results are summarized in Table 1 below.

Table 1: Summary of f2 Similarity Results to Compare [redacted] and Carbatrol® Dissolution Profiles

Strength	[redacted] Batch Numbers (Test Product)	Carbatrol® Batch Numbers (Reference Product)	f2 Similarity Factor
100mg	ODV030145	9A2709B	71
		9A2710B	65
		9A2711B	63
200mg	ODV030143	49M0	81
		58T0	90
		58Y0	90
300mg	ODV030144	68G0	92
		68L0	79
		68S0	80

16 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Shire

Current Approved Carbatrol Label:

Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

Agents that may affect carbamazepine plasma levels:

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels.

Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, valproate. *

CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCL, felbamate, rifampin*, phenobarbital, phenytoin, primidone, theophylline.

*increased levels of the active 10, 11-epoxide

Effect of carbamazepine on plasma levels of concomitant agents:

Carbatrol increases levels of clomipramine HCL, phenytoin and primidone.

Carbatrol induces hepatic CYP activity. Carbatrol causes, or would be expected to cause decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, warfarin.

The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

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/s/

Andre Jackson
11/23/04 01:31:02 PM
BIOPHARMACEUTICS

Sally Yasuda
11/23/04 02:26:24 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21710	Brand Name	[ ]
OCPB Division (I, II, III)	Division I	Generic Name	Carbamazepine ER capsules
Medical Division	Neuropharmacology	Drug Class	Antiepileptic
OCPB Reviewer	Andre Jackson	Indication(s)	Bipolar Disorder
OCPB Team Leader	Ray Baweja	Dosage Form	ER capsules
		Dosing Regimen	400 mg/day given in divided doses BID
Date of Submission	February 13, 2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	October 25, 2004	Sponsor	Shire Pharmaceutical
PDUFA Due Date	December 13, 2004	Priority Classification	1S
Division Due Date	November 22, 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	N/A			
I. Clinical Pharmacology	N/A			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -	N/A			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	x	1	Numerous Journal Articles	
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	N/A			
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	N/A			
Phase 2:				
Phase 3:				
PK/PD:	N/A			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	N/A			
Data rich:				
Data sparse:				
II. Biopharmaceutics	N/A			
Absolute bioavailability:				

Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**N/A**			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**N/A**			
Dissolution:	**x**	**1**		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	**N/A**			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**Journal Articles**			
Total Number of Studies	**N/A**	**2**		

Filability and QBR comments

	"X" if yes	Comments
Application fileable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Is the Dissolution for the new yellow green/blue capsules (mania) the same as for the original teal green/black capsules(epilepsy)? 2. What are the major drug interactions presented in the references for Carbamazepine that should be included in the revised label for [ ]**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21710 HFD-850 (Lee), HFD-120 (Bates), HFD-860 (Mehta, Sahajwalla,Jackson, Baweja), CDR (Biopharm-CDR)

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/s/

Andre Jackson
4/1/04 07:13:45 AM
BIOPHARMACEUTICS

Raman Baweja
4/1/04 09:20:40 AM
BIOPHARMACEUTICS
OCPB NDA Filing and Review Form -- Memo to File

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860 (Dr. Baweja, Dr. Kumi, Copy to Dr. Uppoor			FROM: HFD-120 (Dr. Bates)	
DATE Feb. 20, 2004	IND NO.59,050	NDA NO. 21-710	TYPE OF DOCUMENT new NDA	DATE OF DOCUMENT Feb. 13, 2004
NAME OF DRUG carbamazepine	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG antimanic	DESIRED COMPLETION DATE: Filing Meeting March 31, 2004; action due date December 13, 2004. Review due date will be set at filing meeting.

NAME OF FIRM: Shire Pharmaceutical Development, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW

OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☒ DISSOLUTION
- ☒ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is the carbamazepine product for bipolar. Hybrid paper and electronic submission. Please let the CSO know if we need to have DSI biopharm look at anything, or if the review assignment has changed – thanks!

EDR link below:

\\CDSESUB1\N21710\N_000\2004-02-13

SIGNATURE OF REQUESTER see DFS signature	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
2/20/04 06:29:40 PM

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/s/

Doris Bates
2/20/04 06:30:52 PM

BIOWAIVER REQUEST

The bioequivalence of SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg can be established by *in vitro* testing in accordance with 21 CFR 320.22 (d)(2)(i) – (iii). Based on the following, Shire hereby requests an *in vivo* bioavailability waiver for SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg:

1) SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg has the same qualitative and quantitative components as Carbatrol® (extended-release capsules) 100 mg, 200 mg, and 300 mg.

2) Dissolution profile generated for SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg and Carbatrol (extended-release capsules) 100 mg, 200 mg, and 300 mg demonstrate the comparability of the products.

Included on the following pages are:

1) A comparison of the composition of SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg and Carbatrol (extended-release capsules) 100 mg, 200 mg, and 300 mg.

2) Dissolution results for SPD417 (extended-release capsules) 100 mg, 200 mg, and 300 mg.

3) Dissolution results for Carbatrol (extended-release capsules) 100 mg, 200 mg, and 300 mg.

4) Comparative dissolution f2 similarity plots of SPD417 (extended-release capsules) versus Carbatrol (extended-release capsules) for the 100 mg, 200 mg, and 300 mg strengths.

Quantitative Composition of Carbatrol (100 mg, 200 mg, 300 mg) and SPD417 (100 mg, 200 mg, 300 mg)

Composition of Carbatrol (extended-release capsules) and Intermediate Pellets (%)				
Ingredient	Immediate -Release	Sustained-Release	Enteric-Release	Composite Capsule
Carbamazepine, USP	80.0	69.0	69.0	71.7
Lactose Monohydrate, NF				
Citric Acid, USP (Anhydrous)				
Povidone, USP				
Talc, USP				
Microcrystalline Cellulose, NF				
Triethyl Citrate, NF				
Sodium Lauryl Sulfate, NF				
Polyethylene Glycol				
Colloidal Silicon Dioxide, NF				
Total	100.0	100.0	100.0	100.0
Percentage of Composite Capsule				

Composition of SPD417 (extended-release capsules) and Intermediate Pellets (%)				
Ingredient	Immediate -Release	Sustained-Release	Enteric-Release	Composite Capsule
Carbamazepine, USP	80.0	69.0	69.0	71.7
Lactose Monohydrate, NF				
Citric Acid, USP (Anhydrous)				
Povidone, USP				
Talc, USP				
Microcrystalline Cellulose, NF				
Triethyl Citrate, NF				
Sodium Lauryl Sulfate, NF				
Polyethylene Glycol				
Colloidal Silicon Dioxide, NF				
Total	100.0	100.0	100.0	100.0
Percentage of Composite Capsule				

Dissolution Results for SPD417 (extended-release capsules), 100mg, 200mg, and 300mg (Shire Analysis Reports AR03L038, AR03L037, AR03L039)

Shire Laboratories, Inc.

Analysis Report

AR03L038

PAGE 1 of 2

LOT#:	ODV030145
ACTIVE INGREDIENT:	Carbamazepine
PACKAGING:	[ ]
PRODUCT DESCRIPTION:	SPD417 Extended-Release Capsules, 100mg
SAMPLES:	1
PRODUCT CODE:	BP417-1
SPECIFICATION:	For Information Only
PROJECT:	SPD417

Dissolution

BLB-220-0015
Rev. 00

Date Tested: 30-Dec-03
Reference NB: AL-2147/034

Specification:	Time(Hours)	% Dissolved
	1.0	[
	4.0	
	6.0	
	12.0	]

Percent Dissolved Vessel	1 hr	2 hr	4 hr	6 hr	8 hr	10hr
1	[					
2						
3						
4						
5						
6						]
MAX	[					]
MIN	[					]
MEAN	21	33	48	84	96	102	104

Results: Does not conform to specifications at L1 testing.

Shire Laboratories, Inc.

Analysis Report

AR03L038

PAGE 2 of 2

Dissolution

BLB-220-0015
Rev. 00

Date Tested: 06-Jan-04
Reference NB: AL-2147/070

Specification:	Time(Hours)	% Dissolved
	1.0	[
	4.0	
	6.0	
	12.0	]

Percent Dissolved Vessel	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	[						
2							
3							
4							
5							
6							]
MAX	[						]
MIN	[						]
MEAN	23	35	50	82	95	102	104

Results: Does not conform to specifications at L1 testing.

Results Summary:

	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
Mean	22	34	49	83	96	102	104
Min	[						]
Max	[						]

Results: Conforms to L2 Testing.

Reference: SLI Protocol VP-03-040 lot# ODV030145

Prepared By: [ ] Date: 22Jan04

Reviewed By: [ ] Date: 22 Jan 04

These data are for information only.

Reviewed By: [ ] Date: 22JAN04

cc: [

Shire Laboratories, Inc.

Analysis Report

AR03L037

PAGE 1 of 2

LOT#:	ODV030143
ACTIVE INGREDIENT:	Carbamazepine
PACKAGING:	[ ]
PRODUCT DESCRIPTION:	SPD 417 Extended-Release Capsules, 200mg
SAMPLES:	1
PRODUCT CODE:	BP417-2
SPECIFICATION:	For Information Only
PROJECT:	SPD417

Dissolution

BLB-220-0007
Rev. 00

Date Tested: 07-Jan-04
Reference NB: AL-2147/085

Specification:	Time(Hours)	% Dissolved
	1.0	[
	4.0	
	6.0	
	12.0	]

Percent Dissolved

Vessel	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	[						
2							
3							
4							
5							
6							]
MAX	[						]
MIN	[						]
MEAN	19	30	44	79	92	98	100

Results: Conforms to specifications at L1 testing.

Shire Laboratories, Inc.

Analysis Report

AR03L037

Dissolution

BLB-220-0007
Rev. 00

Date Tested: 07-Jan-04
Reference NB: AL-2147/086

Specification:

Time(Hours)	% Dissolved
1.0	
4.0	
6.0	
12.0	

Percent Dissolved							
Vessel	1 hr	2 hr	4 hr	6 hr	8 hr	10hr	12 hr
1							
2							
3							
4							
5							
6							
MAX	18	30	44	81	94	99	101
MIN	15	25	38	72	85	91	97
MEAN	16	28	42	76	89	95	99

Results: Conforms to specifications at L1 testing.

Results Summary:

L2	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
Mean	18	29	43	78	91	96	100
Min							
Max							

Results: Conforms to L2 Testing.

Reference: SLI Protocol VP-03-040 lot# ODV030143.

Prepared By: ___ Date: 22-Jan-04

Reviewed By: ___ Date: 22 Jan 04

These data are for information only.

Approved By: ___ Date: 22 JAN 04

cc:

Shire Laboratories, Inc.

Analysis Report

AR03L039

LOT#:	ODV030144
ACTIVE INGREDIENT:	Carbamazepine
PACKAGING:	[ ]
PRODUCT DESCRIPTION:	SPD417 Extended-Release Capsules, 300mg
SAMPLES:	1
PRODUCT CODE:	BP417-3
SPECIFICATION:	For Information Only
PROJECT:	SPD417

Dissolution

BLB-220-0007
Rev. 00

Date Tested: 06-Jan-04
Reference NB: AL-2147/075

Specification:

Time(Hours)	% Dissolved
1.0	[
4.0	
6.0	
12.0	]

Percent Dissolved Vessel	1 hr	2 hr	4 hr	6 hr	8 hrs	10hr	12 hr
1	[						
2							
3							
4							
5							
6							]
MAX	[						
MIN	[						]
MEAN	14	23	36	72	84	92	] 3 96

Results: Conforms to specifications at L1 testing.

Shire Laboratories, Inc.

Analysis Report

AR03L039

PAGE 2 of 2

Dissolution

BLB-220-0007
Rev. 00

Date Tested: 14-Jan-04
Reference NB: AL-2147/128

Specification:

Time(Hours)	% Dissolved
1.0	[
4.0	
6.0	
12.0	]

Percent Dissolved Vessel	1 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	[					
2						
3						
4						
5						
6						]
MAX	[					]
MIN	[					]
MEAN	19	29	40	74	86	94	97

Results: Conforms to specifications at L1 testing.

Results Summary:

	1 hr	4 hr	6 hr	8 hr	10 hr	12 hr
Mean	16	26	38	73	85	93	96
Min	[						
Max							]

Results: Conforms to L2 Testing.

Reference: SLI Protocol VP-03-040 lot# ODV030144.

Prepared By: [Date: 22 Jan04

Reviewed By: Date: 22 Jan 04

These data are for information only.

Approved By:] Date: 22JAN04

cc:

Dissolution Results for Carbatrol® (extended-release capsules), 100mg, 200mg, and 300mg

Table 1: Carbatrol® 100mg Dissolution Data for SPD417 Comparability Study

Sample Time Points	Lot 9A2709B (n=18)	Lot 9A2710B (n=12)	Lot 9A2711B (n=12)	Overall Mean (3 Lots)
1-hour	22 21 19 21 21 21 22 18 20 23 22 19 23 20 18 19 19 23 Mean = 21	18 19 18 18 18 16 19 15 19 17 20 19 Mean = 18	17 16 19 19 19 20 20 19 15 19 19 17 Mean = 18	19
2-hour	34 31 30 31 33 32 34 27 32 34 34 31 35 31 30 31 29 36 Mean = 32	29 29 29 30 28 26 30 25 29 27 32 30 Mean = 29	27 25 30 31 30 31 31 30 25 30 29 27 Mean = 29	30
4-hour	48 43 44 44 48 47 49 41 48 49 50 47 50 47 45 45 42 51 Mean = 47	44 41 44 45 43 39 44 38 42 41 46 43 Mean = 43	41 40 45 46 44 45 46 46 39 44 43 42 Mean = 43	44
6-hour	70 65 72 70 79 74 84 82 83 80 86 83 73 75 73 75 74 86 Mean = 77	78 75 75 84 79 76 78 71 77 77 73 75 Mean = 77	68 65 76 82 77 78 78 73 66 82 79 75 Mean = 75	76
8-hour	84 78 89 85 93 90 97 94 97 93 99 97 88 88 89 90 90 98 Mean = 91	94 91 92 96 93 91 91 87 91 91 87 89 Mean = 91	85 81 92 95 91 93 92 86 85 95 91 91 Mean = 90	91
10-hour	93 88 98 96 99 97 103 100 103 100 104 103 98 95 97 98 97 103 Mean = 98	102 99 99 101 99 98 97 94 98 98 94 95 Mean = 98	94 92 99 100 97 101 98 94 95 99 97 99 Mean = 97	98
12-hour	97 94 102 101 101 100 106 102 106 103 106 105 103 99 101 102 101 104 Mean = 102	104 103 102 103 101 100 100 98 102 100 97 97 Mean = 101	99 98 103 103 100 105 101 99 101 101 99 102 Mean = 101	101

References:

1.) NDA 20-712/ S-011 Amendment, dated 15 March 2001, page 012, Table 7. NDA 20-712/S-011, dated 25 July 2000 was subsequently approved on 17 May 2001.

2.) NDA 20-712/ S-007, dated 10 September 1999 and approved 22 December 1999, page 289, Table 1 from TR-99-32.

Appears This Way
On Original

Table 2: Carbatrol® 200mg Dissolution Data for SPD417 Comparability Study

Sample Time Points	Lot 49M0 (n=12)	Lot 58T0 (n=12)	Lot 58Y0 (n=12)	Overall Mean (3 Lots)
1-hour	18 17 19 21 22 17 22 17 15 17 18 16 Mean = 18	18 15 20 16 19 22 19 19 20 17 20 19 Mean = 19	18 18 17 18 17 19 16 17 18 19 18 17 Mean = 18	18
2-hour	29 27 30 33 33 27 33 27 26 29 28 27 Mean = 29	29 24 31 27 32 34 30 30 32 28 31 29 Mean = 30	29 28 28 28 27 30 26 27 27 30 28 26 Mean = 28	29
4-hour	44 42 45 47 48 40 47 41 38 44 42 40 Mean = 43	44 37 46 41 45 48 44 44 46 41 46 43 Mean = 44	44 42 42 41 40 45 40 39 40 43 41 39 Mean = 41	43
6-hour	84 78 81 88 78 73 79 75 69 82 75 79 Mean = 78	85 68 82 72 65 76 77 85 76 72 76 72 Mean = 76	79 80 75 81 76 83 68 73 71 82 69 77 Mean = 76	77
8-hour	97 92 97 100 93 89 94 92 86 97 91 95 Mean = 94	98 84 96 88 77 89 94 98 91 86 91 87 Mean = 90	93 93 89 93 89 95 84 89 86 95 84 89 Mean = 90	91
10-hour	103 100 104 105 100 97 100 98 94 103 97 101 Mean = 100	103 93 101 97 87 96 102 104 99 94 99 94 Mean = 97	100 99 95 99 96 100 93 97 95 100 93 96 Mean = 97	98
12-hour	106 103 107 107 104 99 103 101 99 105 100 103 Mean = 103	105 98 104 102 93 100 105 107 103 99 103 98 Mean = 101	103 102 98 101 100 102 98 100 100 102 98 99 Mean = 100	101

References:

1.) NDA 20-712/ S-011 Amendment, dated 15 March 2001, page 010, Table 5. NDA 20-712/S-011, dated 25 July 2000 was subsequently approved on 17 May 2001.

2.) NDA 20-712/ S-007, dated 10 September 1999 and approved 22 December 1999, page 289, Table 2 from TR-99-32.

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Table 3: Carbatrol® 300mg Dissolution Data for SPD417 Comparability Study				
Sample Time Points	Lot 68G0 (n=12)	Lot 68L0 (n=12)	Lot 68S0 (n=12)	Overall Mean (3 Lots)
1-hour	14 18 20 17 17 16 17 16 16 20 18 17 Mean = 17	17 16 16 20 18 20 16 19 18 19 13 18 Mean = 18	14 15 15 16 15 16 15 16 12 16 13 16 Mean = 15	17
2-hour	24 29 30 27 25 27 27 25 27 31 28 27 Mean = 27	26 26 27 29 28 30 26 29 27 29 23 26 Mean = 27	23 24 24 26 26 26 24 25 20 25 21 25 Mean = 24	26
4-hour	37 41 42 39 37 40 39 37 40 42 40 39 Mean = 39	38 38 41 41 41 41 38 41 40 40 35 38 Mean = 39	35 36 37 38 39 38 36 37 34 38 35 37 Mean = 37	38
6-hour	71 73 72 72 70 72 67 75 73 69 74 73 Mean = 72	70 71 74 77 73 69 70 72 74 77 66 75 Mean = 72	65 65 64 67 74 73 68 70 68 74 70 64 Mean = 69	71
8-hour	86 85 84 87 85 86 80 87 88 83 90 89 Mean = 86	85 86 87 91 87 82 85 87 94 93 82 93 Mean = 88	78 82 78 80 89 86 83 82 82 87 83 79 Mean = 82	85
10-hour	92 90 92 89 94 90 86 94 93 93 95 97 Mean = 92	92 96 95 99 94 91 97 94 98 100 91 99 Mean = 96	86 92 87 85 96 94 92 92 89 95 91 87 Mean = 91	93
12-hour	98 96 97 99 99 98 93 98 97 97 99 98 Mean = 97	97 100 99 103 95 96 97 101 102 111 95 104 Mean = 100	91 98 92 88 99 97 96 90 89 98 96 93 Mean = 94	97

References:

1.) NDA 20-712/ S-011 Amendment, dated 15 March 2001, page 010, Table 5. NDA 20-712/S-011, dated 25 July 2000 was subsequently approved on 17 May 2001.

2.) NDA 20-712/ S-007, dated 10 September 1999 and approved 22 December 1999, page 289, Table 3 from TR-99-32.

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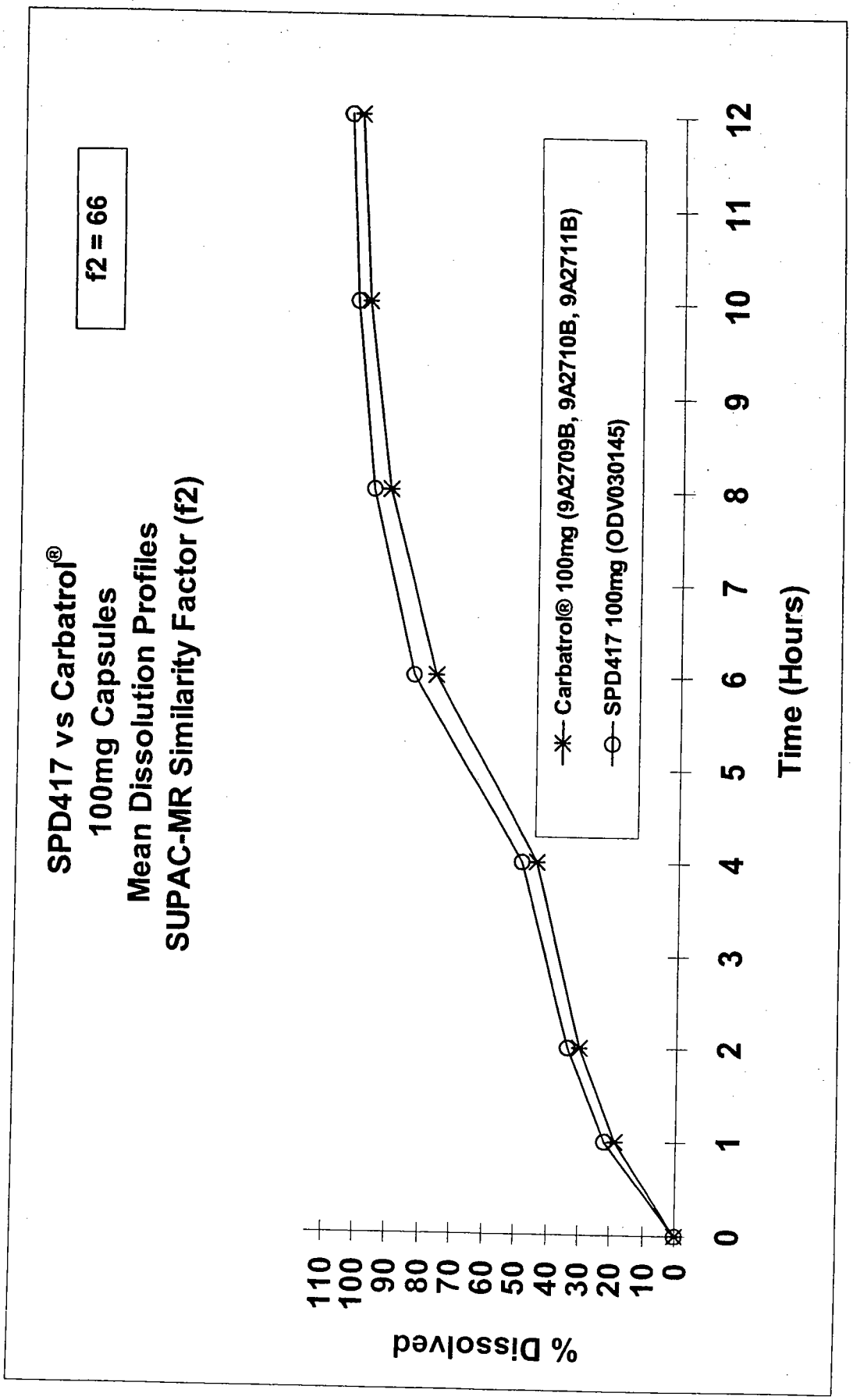
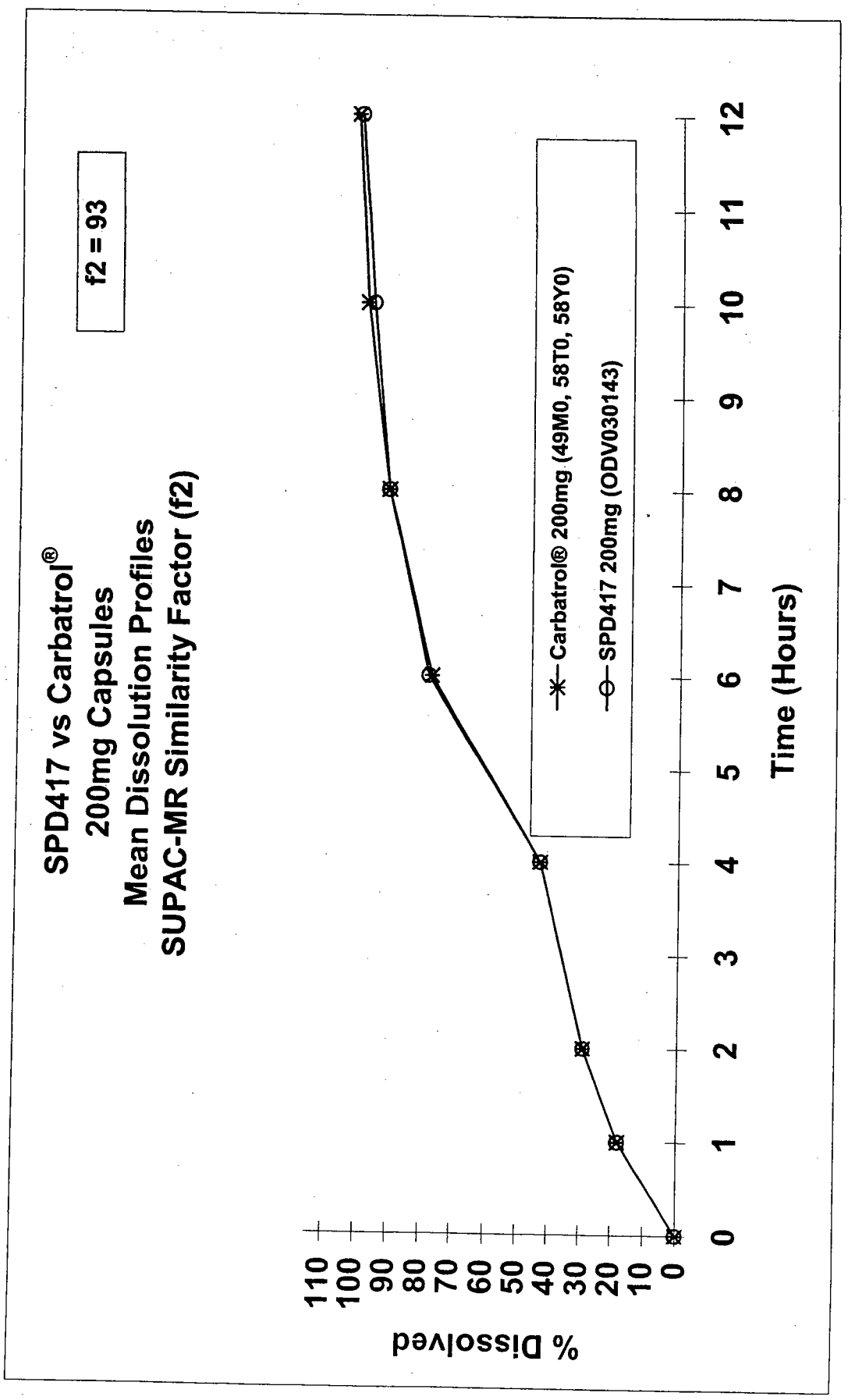
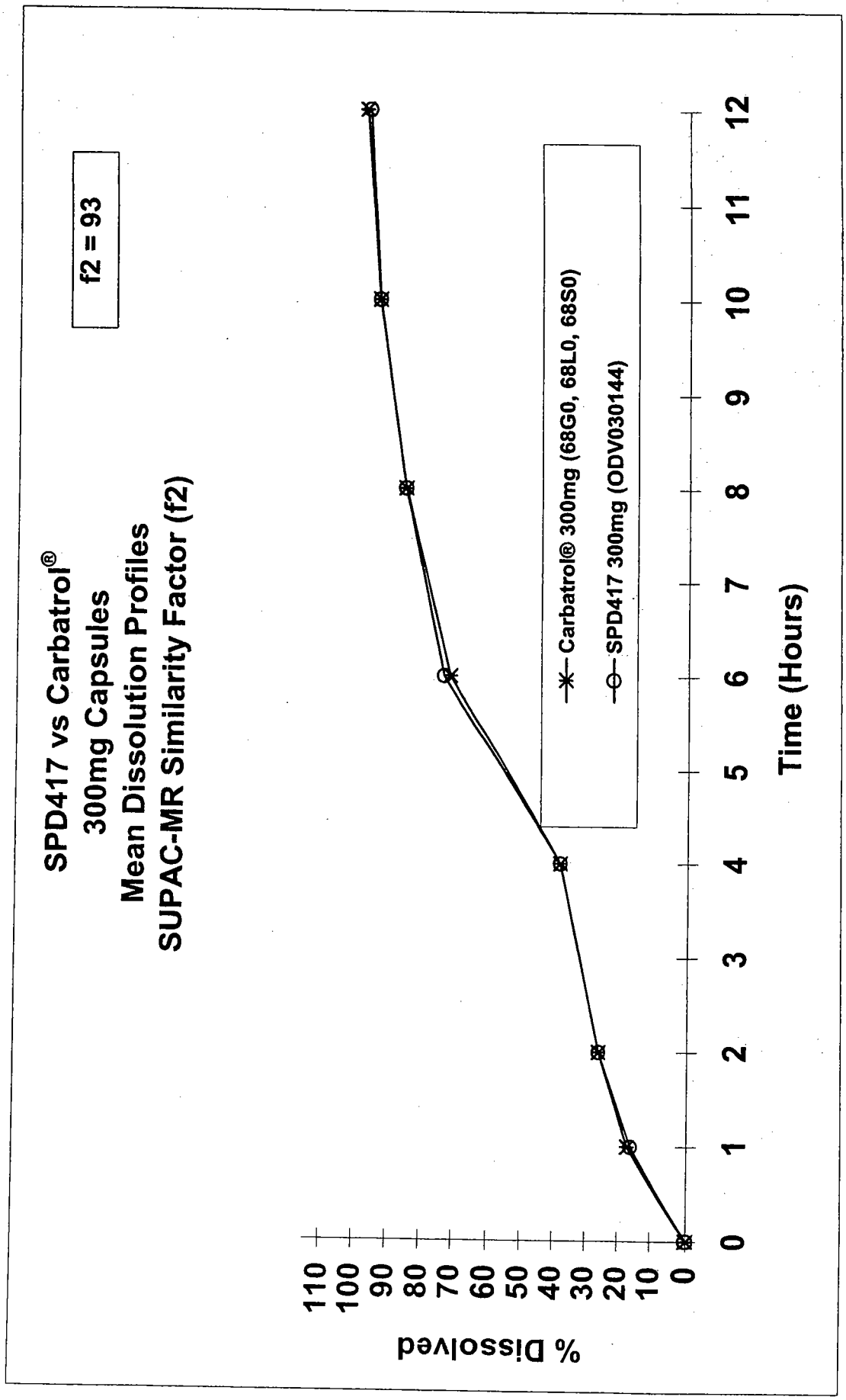
Comparative Dissolution f2 Similarity Plots of SPD417 (extended-release capsules) versus Carbatrol® (extended-release capsules) for the 100mg, 200mg, and 300mg Strengths


SPD417 vs Carbatrol®
100mg Capsules
Mean Dissolution Profiles
SUPAC-MR Similarity Factor (f2)
f2 = 66
Carbatrol® 100mg (9A2709B, 9A2710B, 9A2711B)
SPD417 100mg (ODV030145)
% Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (Hours)


SPD417 vs Carbatrol®
200mg Capsules
Mean Dissolution Profiles
SUPAC-MR Similarity Factor (f2)
f2 = 93
Carbatrol® 200mg (49M0, 58T0, 58Y0)
SPD417 200mg (ODV030143)
% Dissolved
0
10
20
30
40
50
60
70
80
90
100
110
Time (Hours)
0
1
2
3
4
5
6
7
8
9
10
11
12


SPD417 vs Carbatrol®
300mg Capsules
Mean Dissolution Profiles
SUPAC-MR Similarity Factor (f2)
f2 = 93
Carbatrol® 300mg (68G0, 68L0, 68S0)
SPD417 300mg (ODV030144)
% Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (Hours)

Bates, Doris J

From: Bates, Doris J

Sent: Thursday, December 02, 2004 2:39 PM

To: Bates, Doris J

Subject: FW: NDA 21-710: Revised PT Labeling Language.

-----Original Message-----
From: Fisher, J Edward
Sent: Thursday, December 02, 2004 1:54 PM
To: Bates, Doris J
Subject: RE: NDA 21-710: Draft Approval Letter. Please see Message.

Doris, don't hate me, but I have another slight change if it's not too late:

Mechanism of Action

The mechanism(s) of action of carbamazepine in the treatment of bipolar disorder has not been elucidated. Although numerous pharmacological effects of carbamazepine have been described in the published literature (e.g., modulation of ion channels [sodium and calcium], receptor-mediated neurotransmission [GABAergic, glutamatergic, and monoaminergic], and intracellular signaling pathways in experimental preparations), the contribution of these effects to the efficacy of carbamazepine in bipolar disorder is unknown.

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